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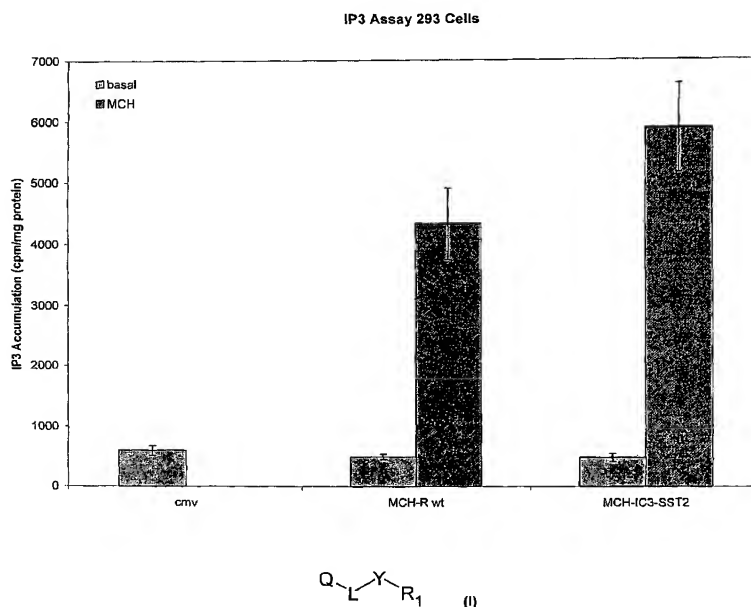
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[Continued on next page]

(54) Title: MCH RECEPTOR ANTAGONISTS



(57) Abstract: The present invention relates to novel compounds of the formula (I) which act as MCH receptor antagonists. These compositions are useful in pharmaceutical compositions whose use includes prophylaxis or treatment of obesity, obesity related disorders, anxiety, or depression.



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MCH RECEPTOR ANTAGONISTS

Field of the Invention

The present invention relates to compounds which act as antagonists for MCH receptors and to the use of these compounds in pharmaceutical compositions.

Background of the Invention

Melanin Concentrating Hormone (MCH), a cyclic peptide, has been identified as the endogenous ligand of the orphan G-protein coupled receptor SLC-1. See, for example, Shimomura et al., *Biochem. Biophys. Res. Commun.* 261, 622-26 (1999). Studies have indicated that MCH acts as a neurotransmitter/neuromodulator to alter a number of behavioral responses such as feeding habits. For example, injection of MCH into rats has been reported to increase their consumption of food. Reports indicate that genetically engineered mice which lack MCH show lower body weight and increased metabolism. See Saito et al., *TEM*, vol. 11, 299 (2000). As such, the literature suggests that discovery of MCH antagonists that interact with SCL-1 expressing cells will be useful in developing obesity treatments. See Shimomura et al., *Biochem. Biophys. Res. Commun.* 261, 622-26 (1999).

G protein-coupled receptors (GPCRs) share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane. The fourth and fifth transmembrane helices are joined on the extracellular side of the membrane by a strand of amino acids that forms a relatively large loop. Another larger loop, composed primarily of hydrophilic amino acids, joins transmembrane helices five and six on the intracellular side of the membrane. The carboxy terminus of the receptor lies intracellularly, and the amino terminus lies in the extracellular space. It is thought that the loop joining helices five and six,

as well as the carboxy terminus, interact with the G protein. Currently, Gq, Gs, Gi, and Go are G proteins that have been identified as possible proteins that interact with the receptor.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different states or conformations: an “inactive” state and an “active” state. A receptor in an inactive state is unable to link to the intracellular transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway and produces a biological response.

A receptor may be stabilized in an active state by an endogenous ligand or an exogenous agonist ligand. Recent discoveries, including but not exclusively limited to, modifications to the amino acid sequence of the receptor, provide alternative mechanisms other than ligands to stabilize the active state conformation. These approaches effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent approaches is termed “constitutive receptor activation.” In contrast, antagonists can competitively bind to the receptor at the same site as agonists, but do not activate the intracellular response initiated by the active form of the receptor, and therefore inhibit the intracellular responses by agonists.

Certain 2-aminoquinazoline derivatives have been reported to be NPY antagonists which are said to be effective in the treatment of disorders and diseases associated with the NPY receptor subtype Y5. See PCT Patent Application 97/20823. Quinazoline derivatives have also been found to be useful by enhancing antitumor activity. See PCT Patent Application 92/07844.

Recently, our current knowledge of human obesity has advanced dramatically. Previously, obesity was viewed as an oppugnant behavior of inappropriate eating in the setting of appealing foods. Studies of animal models of obesity, biochemical alterations in both humans and animals, and the complex interactions of psychosocial and cultural factors that create receptiveness to human obesity indicate that this disease in humans is multifaceted and deeply entrenched in biologic systems. Thus, it is almost certain that obesity has multiple causes and that there are different types of obesity. Not only does MCHR1 antagonist have potent and durable anti-obesity effects in rodents, it has surprising antidepressant and anxiolytic properties as well (Borowsky et al., *Nature Medicine*, 8, 825-830, 2002). MCHR1 antagonists have been reported to show antidepressant and anxiolytic activities in rodent models such as social interaction, forced swimming test and ultrasonic

vocalization. These findings indicate that MCHR1 antagonists could be useful for treatment of obesity patients with multiple causes. Moreover, MCHR1 antagonists could be used to treat subjects not only with obesity, but also those with depression and anxiety. These advantages make it different from NPY receptor antagonists, with which anxiogenic-like activity may be expected, as NPY itself has anxiolytic-like effect.

Obesity is also regarded as a chronic disease and the possibly of long-term treatment is a concept that is receiving more attention. In this context, it is noteworthy that the depletion of MCH leads to hypophagia as well as leanness (Shimada et al., *Nature*, 396, 670-674, 1998). By contrast, NPY (Erickson et al., *Nature*, 381, 415-418, 1996), as well as the Y1 (Pedrazzini et al., *Nature Medicine*, 4, 722-726, 1998) and Y5 receptors (Marsh et al., *Nature Medicine*, 4, 718-721, 1998), disrupted mice maintained a stable body weight or rather became obese. Considering the above reports, MCHR1 antagonists may be more attractive than Y1 or Y5 receptor antagonists in terms of long-term treatment of obese patients.

An increasing number of children and adolescents are overweight. Although not all overweight children will necessarily become overweight adults, the growing occurrence of obesity in childhood is likely to be reflected in increasing obesity in adult years. The high prevalence of obesity in our adult population and the likelihood that the nation of the future will be even more obese demands a re-examination of the health implications of this disease. See, Health Implications of Obesity. NIH Consens. Statement Online 1985 Feb 11-13; 5(9):1-7.

“Clinical obesity” is a measurement of the excess body fat relative to lean body mass and is defined as a body weight more than 20% above the ideal body weight. Recent estimates suggest that 1 in 2 adults in the United States is clinically obese, an increase of more than 25% over the past decades. Flegal M.D. et al., 22 *Int. J. Obes. Relat. Metab. Disor.* 39 (1998). Both overweight conditions and clinical obesity are a major health concerns worldwide, in particular because clinical obesity is often accompanied by numerous complications, *i.e.*, hypertension and Type II diabetes, which in turn can cause coronary artery disease, stroke, late-stage complications of diabetes and premature death. (See, e.g., Nishina P.M. et al., 43 *Metab.* 554 (1994)).

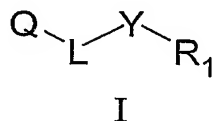
Although the etiologic mechanisms underlying obesity require further clarification, the net effect of such mechanisms leads to an imbalance between energy intake and

expenditure. Both genetic and environmental factors are likely to be involved in the pathogenesis of obesity. These include excess caloric intake, decreased physical activity, and metabolic and endocrine abnormalities.

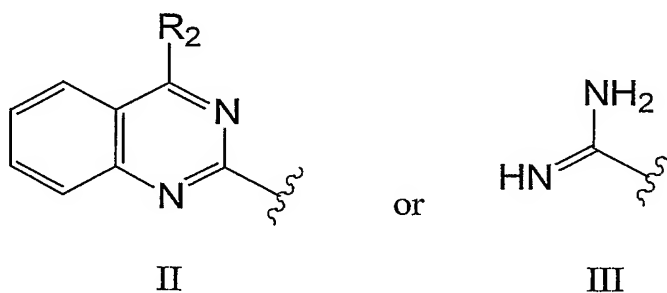
Treatment of overweight conditions and clinical obesity via pharmaceutical agents are not only of importance with respect to the conditions themselves, but also with respect to the possibility of preventing other diseases that are associated with, *e.g.*, clinical obesity, as well as enhancement of the positive feeling of "self" that often accompanies those who are overweight or clinically obese and who encounter a significant reduction in body weight. Given the foregoing discussion, it is apparent that compounds which help in the treatment of such disorders would be useful and would provide an advance in both research and clinical medicine. The present invention is directed to these, as well as other, important ends.

Summary of the Invention

The present invention, in one aspect, relates to compounds represented by Formula I:



or a pharmaceutically acceptable salt or prodrug thereof, wherein Q is



R₁ represents

(i) C₁-C₁₆ alkyl,

C₁-C₁₆ alkyl substituted by substituent(s) independently selected from

- halogen,
- hydroxy,
- oxo,

- C₁-C₃ alkoxy,
- C₁-C₃ alkoxy substituted by substituent(s) independently selected from
 - carbocyclic aryl,
 - heterocyclyl,
 - heterocyclyl substituted by C₁-C₃ alkyl,
- C₁-C₃ alkylcarbonyloxy,
- carbocyclyloxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by C₁-C₃ alkoxy,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - oxo,
 - mono- or di-C₁-C₃ alkylamino,
 - mono- or di-C₁-C₃ alkylamino substituted by carbocyclic aryl,
 - mono- or di-C₁-C₃ alkylamino substituted by halogenated carbocyclic aryl,
 - carbocyclic arylcarbonylamino,
 - halogenated carbocyclic arylcarbonylamino,
- heterocyclyloxy,
- heterocyclyloxy substituted by C₁-C₃ alkyl,
- substituted heterocyclyl-ethylideneaminooxy,
- C₁-C₃ alkoxycarbonyl,
- C₁-C₃ alkoxycarbonyl substituted by carbocyclic aryl,
- mono- or di-C₁-C₃ alkylaminocarbonyl,
- mono- or di-C₁-C₃ alkylamino,
- mono- or di-C₁-C₃ alkylamino substituted by substituent(s) independently selected from
 - cyano,
 - carbocyclic aryl,
 - heterocyclyl,

- mono- or di-carbocyclic arylamino,
- mono- or di-carbocyclic arylamino substituted by substituent(s) independently selected from
 - hydroxy,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkylcarbonylamino,
 - C₁-C₃ alkylcarbonylamino substituted by substituent(s) independently selected from
 - C₁-C₃ alkylcarbonylamino,
 - carbocyclic arylcarbonylamino,
 - heterocyclyl,
 - C₁-C₄ alkoxy carbonylamino,
 - heterocyclyl carbonylamino,
 - carbocyclic arylsulfonylamino,
 - carbocyclic arylsulfonylamino substituted by substituent(s) independently selected from
 - nitro,
 - C₁-C₃ alkyl,
 - mono- or di-C₁-C₃ alkylamino,
 - C₁-C₃ alkylthio,
 - C₁-C₃ alkylthio substituted by substituent(s) independently selected from
 - mono- or di-carbocyclic arylaminocarbonyl,
 - halogenated mono- or di-carbocyclic arylaminocarbonyl,
 - mono- or di-carbocyclic arylamino,
 - halogenated mono- or di-carbocyclic arylamino,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkoxy,
 - carbocyclic arylthio,
 - carbocyclic arylthio substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - carbocyclic arylsulfonyl,

- halogenated carbocyclic arylsulfonyl,
- heterocyclylthio,
- heterocyclylthio substituted by substituent(s) independently selected from
 - nitro,
 - C₁-C₃ alkyl,
 - C₃-C₆ cycloalkyl,
 - C₃-C₆ cycloalkyl substituted by C₁-C₃ alkyl,
 - C₃-C₆ cycloalkenyl,
- carbocyclyl,
- carbocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - C₂-C₃ alkenyl,
 - C₂-C₃ alkenyl substituted by carbocyclic aryl,
 - C₂-C₃ alkenyl substituted by carbocyclic aryl substituted C₁-C₃ alkylsulfinyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - oxo,
 - carbocyclic aryl,
 - heterocyclyl,
 - mono- or di-carbocyclic arylamino,
 - mono- or di-carbocyclic arylamino substituted by substituent(s) independently selected from
 - halogen,

- nitro,
- C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- halogenated C₁-C₃ alkoxy,
- C₁-C₄ alkoxy,
- C₁-C₄ alkoxy substituted by substituent(s) independently selected from
- halogen,
- carbocyclic aryl,
- carbocyclic aryloxy,
- C₁-C₃ alkoxycarbonyl,
- C₁-C₃ alkylcarbonyloxy,
- mono- or di-C₁-C₃ alkylamino,
- mono- or di-carbocyclic arylamino,
- halogenated mono- or di-carbocyclic arylamino,
- mono- or di-carbocyclic arylaminocarbonyl,
- mono- or di-carbocyclic arylaminocarbonyl substituted by substituent(s) independently selected from
- halogen,
- nitro,
- C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- halogenated C₁-C₃ alkoxy,
- mercapto,
- C₁-C₃ alkylthio,
- halogenated C₁-C₃ alkylthio,
- C₁-C₃ alkylsulfonyl,
- C₃-C₆ cycloalkyl,
- carbocyclic aryl,
- heterocyclyl,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- hydroxy,

- C₁-C₃ alkyl,
 - C₁-C₃ alkyl substituted by carbocyclic aryl,
 - C₁-C₃ alkoxy,
 - C₁-C₃ alkoxy substituted by carbocyclic aryl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
- (ii) C₂-C₈ alkenyl,
- C₂-C₈ alkenyl substituted by substituent(s) independently selected from
- halogen,
 - oxo,
 - C₁-C₃ alkoxy,
 - C₁-C₃ alkoxy substituted by carbocyclic aryl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - nitro,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - halogenated C₁-C₃ alkoxy,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - hydroxy,
 - nitro,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
- (iii) C₂-C₄ alkynyl,
- C₂-C₄ alkynyl substituted by carbocyclic aryl,
- (iv) C₃-C₆ cycloalkyl,
- C₃-C₆ cycloalkyl substituted by substituent(s) independently selected from
- C₁-C₃ alkyl,

•C₁-C₃ alkyl substituted by substituent(s) independently selected from

•hydroxy,

•oxo,

•carbocyclic aryl,

•mono- or di-C₁-C₃ alkylamino,

•mono- or di-C₁-C₃ alkylamino substituted by carbocyclic aryl,

•carbocyclic arylcarbonylamino,

•carbocyclic aryl,

(v) C₃-C₆ cycloalkyl,

C₃-C₆ cycloalkyl substituted by C₁-C₃ alkyl,

(vi) carbocyclyl,

carbocyclyl substituted by substituent(s) independently selected from

•hydroxy,

•nitro,

(vii) carbocyclic aryl,

carbocyclic aryl substituted by substituent(s) independently selected from

•halogen,

•hydroxy,

•cyano,

•nitro,

•C₁-C₉ alkyl,

•C₁-C₉ alkyl substituted by substituent(s) independently selected from

•halogen,

•hydroxy,

•oxo,

•C₁-C₃ alkoxy,

•carbocyclic aryloxy,

•mono- or di-C₁-C₃ alkylamino-N-oxy,

•mono- or di-C₁-C₃ alkylamino,

•mono- or di-C₁-C₃ alkylamino substituted by carbocyclic aryl,

•mono- or di-carbocyclic arylamino,

•carbocyclylimino,

- carbocyclylimino substituted by carbocyclic aryl,
- mono- or di-carbocyclic arylamino,
- mono- or di-carbocyclic arylamino substituted by C₁-C₃ alkoxy,
- mono- or di-carbocyclic arylaminocarbonyl,
- mono- or di-carbocyclic arylaminocarbonyl substituted by C₁-C₃ alkoxy,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
 - heterocyclyl,
 - heterocyclyl substituted by C₁-C₃ alkyl,
 - C₂-C₃ alkenyl,
 - C₂-C₃ alkenyl substituted by carbocyclic aryl,
 - C₁-C₉ alkoxy,
 - C₁-C₉ alkoxy substituted by substituent(s) independently selected from
 - hydroxy,
 - halogen,
 - carboxy,
 - mono- or di-C₁-C₃ alkylamino,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
 - C₂-C₃ alkenyloxy,
 - C₁-C₃ alkylcarbonyloxy,

- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₄ alkyl,
 - halogenated C₁-C₄ alkyl,
 - C₁-C₃ alkoxy,
- heterocyclyloxy,
- heterocyclyloxy substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
- (carbocyclic aryl)S(O)₂O,
- carboxy,
- C₁-C₃ alkoxycarbonyl,
- mono- or di-C₁-C₃ alkylaminocarbonyl,
- mono- or di-C₁-C₃ alkylaminocarbonyl substituted by carbocyclic aryl,
- mono- or di-carbocyclic arylaminocarbonyl,
- mono- or di-carbocyclic arylaminocarbonyl substituted by C₁-C₃ alkyl,
- amino,
- mono- or di-C₁-C₄ alkylamino,
- mono- or di-C₁-C₄ alkylamino substituted by cyano,
- mono- or di-carbocyclic arylamino,
- C₁-C₃ alkynylcarbonylamino,
- C₁-C₃ alkynylcarbonylamino substituted by carbocyclic aryl,
- carbocyclic arylsulfonylamino,
- carbocyclic arylsulfonylamino substituted by C₁-C₃ alkyl,
- (carbocyclic aryl)NHC(O)NH,
- (carbocyclic aryl)NHC(O)NH substituted by C₁-C₃ alkoxy,
- (carbocyclic aryl)NHC(O)NH substituted by halogenated C₁-C₃ alkoxy,
- carbocyclic aryl diazo,
- carbocyclic aryl diazo substituted by mono- or di- C₁-C₃ alkylamino,

- C₁-C₃ alkylthio,
- halogenated C₁-C₃ alkylthio,
- carbocyclic arylthio,
- carbocyclic arylthio substituted by substituent(s) independently selected from
 - halogen,
 - cyano,
 - C₁-C₃ alkyl,
- heterocyclylthio,
- C₁-C₃ alkylsulfonyl,
- mono- or di-C₁-C₃ alkylaminosulfonyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - C₁-C₇ alkyl,
 - halogenated C₁-C₇ alkyl,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
- (viii) heterocyclyl,
or heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - oxo,
 - C₁-C₃ alkylcarbonyloxy,
 - carbocyclic arylcarbonylamino,

- halogenated carbocyclic arylcarbonylamino,
- C₁-C₃ alkoxycarbonyl,
- C₁-C₃ alkylthio,
- C₁-C₃ alkylthio substituted by carbocyclic aryl,
- C₁-C₃ alkylthio substituted by halogenated carbocyclic aryl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - C₁-C₃ alkoxy substituted by carbocyclic aryl,
 - carbocyclic aryloxy,
 - carbocyclic aryloxy substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - mono- or di-C₁-C₃ alkylamino,
 - C₁-C₄ alkylcarbonylamino,
 - C₁-C₃ alkylthio,
 - C₁-C₃ alkenylthio,
 - carbocyclic arylthio,
 - halogenated carbocyclic arylthio,
 - carbocyclic arylthio substituted by C₁-C₃ alkoxycarbonyl,
 - heterocyclylthio,
 - heterocyclylthio substituted by C₁-C₃ alkyl,
 - C₁-C₃ alkylsulfonyl,
 - carbocyclic arylsulfonyl,
 - halogenated carbocyclic arylsulfonyl,

- carbocyclic arylsulfonyl substituted by C₁-C₄ alkyl,
- C₁-C₃ alkoxy carbonyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - halogenated C₁-C₃ alkoxy,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - C₁-C₃ alkoxy carbonyl;

R₂ is -NHNH₂, -NHNHBoc, -N(R_{2a})(R_{2b}), morpholino, 4-acetyl-piperazyl, or 4-phenyl-piperazyl;

wherein R_{2a} is H or C₁-C₃ alkyl;

R_{2b} is C₁-C₄ alkyl, C₁-C₄ alkyl substituted by substituent(s) independently selected from

- hydroxy,
- C₁-C₃ alkoxy,
- amino,
- NHBoc,
- C₃-C₆ cycloalkyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - SO₂NH₂,

•heterocyclyl,

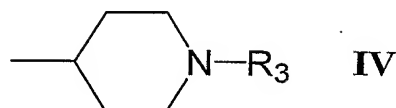
C₃-C₆ cycloalkyl, carbocyclic aryl, carbocyclic aryl substituted by substituent(s)
independently selected from

•halogen,

•C₁-C₃ alkyl,

•C₁-C₃ alkoxy,

or a group of Formula IV;



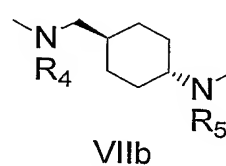
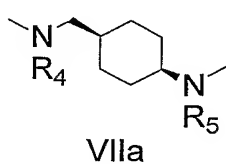
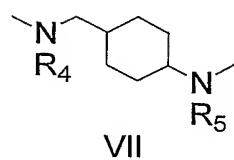
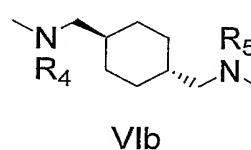
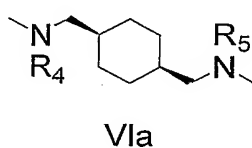
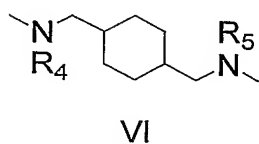
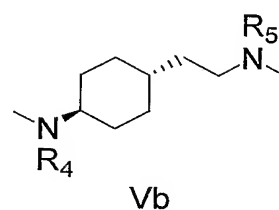
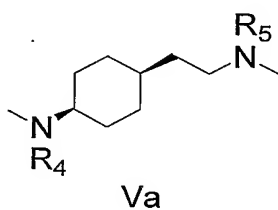
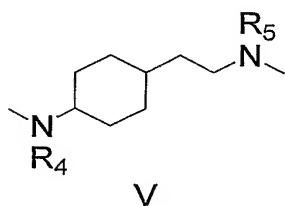
wherein Boc is carbamic acid *tert*-butyl ester and R₃ is C₁-C₃ alkyl or C₁-C₃ alkyl substituted by substituent(s) independently selected from

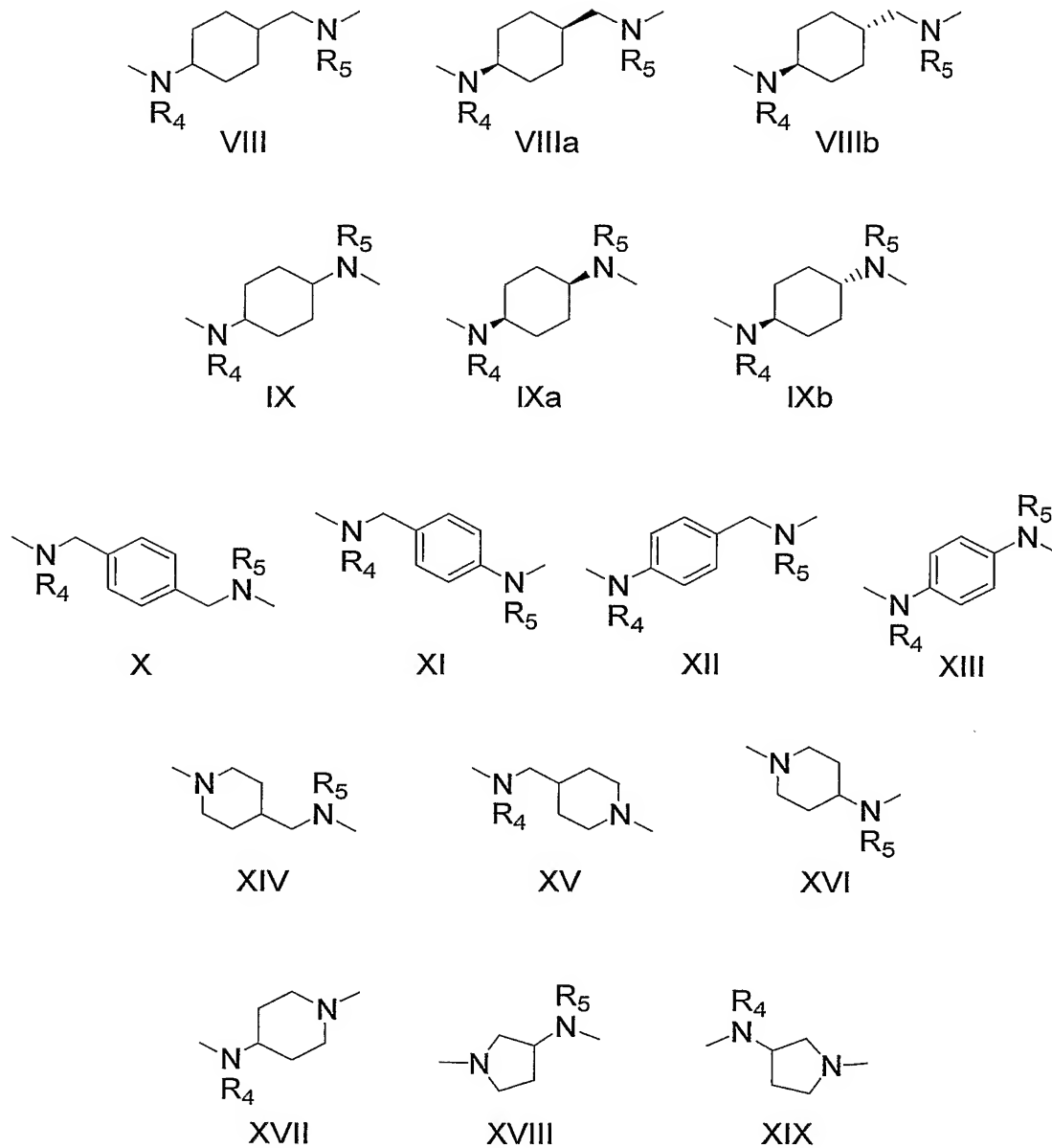
•carbocyclic aryl,

•halogenated carbocyclic aryl,

•carbocyclic aryl substituted by C₁-C₃ alkoxy;

L is selected from Formula V - XIX;





wherein R₄ is H or C₁-C₃ alkyl;

R₅ is H, C₁-C₃ alkyl, or C₁-C₃ alkyl substituted by a substituted carbocyclic aryl;

Y is -S(O)₂-, -C(O)-, or -(CH₂)_m;

m is 0 or 1;

wherein carbocyclic aryl is phenyl, naphthyl, anthranyl, biphenyl, or phenanthryl;

carbocyclyl is 10,11-dihydro-5-oxo-dibenzo[a,d]cycloheptyl, 1-oxo-indanyl, 7,7-

dimethyl-2-oxo-bicyclo[2.2.1]heptyl, 9*H*-fluorenyl, 9-oxo-fluorenyl, acenaphthyl, anthraquinonyl, *C*-fluoren-9-ylidene, indanyl, indenyl, 1,2,3,4-tetrahydro-naphthyl, or bicyclo[2.2.1]hepteny;

heterocyclyl is 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,2-dihydro-3-oxo-pyrazolyl, 1,3,4-thiadiazolyl, 1,3-dioxo-isoindolyl, 1,3-dioxolanyl, 1*H*-indolyl, 1*H*-pyrrolo[2,3-*c*]pyridyl, 1*H*-pyrrolyl, 1-oxo-3*H*-isobenzofuranyl, 2,2',5',2"-terthiophenyl, 2,2'-bithiophenyl, 2,3-dihydro-1-oxo-isoindolyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2,3-dihydro-benzofuryl, 2,4-dihydro-3-oxo-pyrazolyl, 2*H*-benzopyranyl, 2-oxo-benzopyranyl, 2-oxo-pyrrolidinyl, 3,4-dihydro-2*H*-benzo[1,4]oxazinyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepinyl, 4*H*-benzo[1,3]dioxinyl, 4*H*-benzopyranyl, 4-oxo-1,5,6,7-tetrahydro-indolyl, 4-oxo-3,4-dihydro-phthalazinyl, 4-oxo-benzopyranyl, 9,10,10-trioxo-thioxanthenyl, 9*H*-carbazolyl, 9*H*-xanthenyl, azetidiny, benzimidazolyl, benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[*b*]thienyl, benzofuryl, benzothiazolyl, cinnolyl, furyl, imidazo[2,1-*b*]thiazolyl, imidazolyl, isoxazolyl, morpholino, morpholinyl, oxazolyl, oxolanyl, piperazyl, piperidyl, piridyl, pyrazolo[5,1-*b*]thiazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolidyl, quinolyl, quinoxalyl, thiazolidyl, thiazolyl, thienyl, thiolanyl, 2,3-dihydro-benzofuryl, tetrahydro-thienyl, or benzofuranyl;

halogen is fluoro, chloro, bromo, or iodo.

Preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₀ alkyl,

C₁-C₁₀ alkyl substituted by substituent(s) independently selected from

•halogen,

•oxo,

•C₁-C₃ alkoxy,

•C₁-C₃ alkoxy substituted by carbocyclic aryl,

•C₁-C₃ alkylcarbonyloxy,

•carbocyclyloxy,

•carbocyclic aryloxy,

•carbocyclic aryloxy substituted by substituent(s) independently selected from

- halogen,
- nitro,
- C₁-C₄ alkyl,
- C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - oxo,
 - carbocyclic arylcarbonylamino,
 - halogenated carbocyclic arylcarbonylamino,
 - heterocycloxy,
 - heterocycloxy substituted by C₁-C₃ alkyl,
 - substituted heterocyclyl-ethylideneaminoxy,
 - C₁-C₃ alkoxy carbonyl,
 - C₁-C₃ alkoxy carbonyl substituted by carbocyclic aryl,
 - mono- or di-C₁-C₃ alkylaminocarbonyl,
 - mono- or di-carbocyclic arylamino,
 - mono- or di-carbocyclic arylamino substituted by hydroxy,
 - C₁-C₃ alkylcarbonylamino,
 - C₁-C₃ alkylcarbonylamino substituted by substituent(s) independently selected from
 - C₁-C₃ alkylcarbonylamino,
 - carbocyclic arylcarbonylamino,
 - heterocyclyl,
 - C₁-C₄ alkoxy carbonylamino,
 - heterocyclyl carbonylamino,
 - carbocyclic arylsulfonylamino,
 - carbocyclic arylsulfonylamino substituted by substituent(s) independently selected from
 - nitro,
 - C₁-C₃ alkyl,
 - mono- or di-C₁-C₃ alkylamino,
 - C₁-C₃ alkylthio,
 - C₁-C₃ alkylthio substituted by substituent(s) independently selected from
 - mono- or di-carbocyclic arylaminocarbonyl,
 - halogenated mono- or di-carbocyclic arylaminocarbonyl,
 - carbocyclic aryl,

- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkoxy,
- carbocyclic arylthio,
- carbocyclic arylthio substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
- carbocyclic arylsulfonyl,
- halogenated carbocyclic arylsulfonyl,
- heterocyclylthio,
- heterocyclylthio substituted by substituent(s) independently selected from
 - nitro,
 - C₁-C₃ alkyl,
 - C₃-C₆ cycloalkyl,
 - C₃-C₆ cycloalkyl substituted by C₁-C₃ alkyl,
 - C₃-C₆ cycloalkenyl,
- carbocyclyl,
- carbocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - C₂-C₃ alkenyl,
 - C₂-C₃ alkenyl substituted by carbocyclic aryl,
 - C₂-C₃ alkenyl substituted by carbocyclic aryl substituted C₁-C₃ alkylsulfinyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - oxo,

- carbocyclic aryl,
- heterocyclyl,
- C₁-C₄ alkoxy,
- C₁-C₄ alkoxy substituted by substituent(s) independently selected from
- halogen,
- carbocyclic aryl,
- carbocyclic aryloxy,
- C₁-C₃ alkylcarbonyloxy,
- mono- or di-carbocyclic arylamino,
- halogenated mono- or di-carbocyclic arylamino,
- mono- or di-carbocyclic arylaminocarbonyl,
- mono- or di-carbocyclic arylaminocarbonyl substituted by substituent(s) independently selected from
- halogen,
- nitro,
- C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- halogenated C₁-C₃ alkoxy,
- mercapto,
- C₁-C₃ alkylthio,
- halogenated C₁-C₃ alkylthio,
- C₁-C₃ alkylsulfonyl,
- C₃-C₆ cycloalkyl,
- carbocyclic aryl,
- heterocyclyl,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- hydroxy,
- C₁-C₃ alkyl,
- C₁-C₃ alkyl substituted by carbocyclic aryl,
- C₁-C₃ alkoxy,
- C₁-C₃ alkoxy substituted by carbocyclic aryl,

- carbocyclic aryl,
- halogenated carbocyclic aryl,
- (ii) C₂-C₆ alkenyl,
C₂-C₆ alkenyl substituted by substituent(s) independently selected from
 - oxo,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - halogenated C₁-C₃ alkoxy,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - hydroxy,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
- (iii) C₃-C₆ cycloalkyl,
C₃-C₆ cycloalkyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,
 - C₁-C₃ alkyl substituted by substituent(s) independently selected from
 - oxo,
 - carbocyclic aryl,
 - carbocyclic arylcarbonylamino,
 - carbocyclic aryl,
- (iv) carbocyclyl,
carbocyclyl substituted by nitro,
- (v) carbocyclic aryl,
carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,

- cyano,
- nitro,
- C₁-C₉ alkyl,
- C₁-C₉ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - oxo,
 - carbocyclic aryloxy,
 - carbocyclylimino,
 - carbocyclylimino substituted by carbocyclic aryl,
 - mono- or di-carbocyclic arylaminocarbonyl,
 - mono- or di-carbocyclic arylaminocarbonyl substituted by C₁-C₃ alkoxy,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
 - heterocyclyl,
 - heterocyclyl substituted by C₁-C₃ alkyl,
- C₁-C₇ alkoxy,
- C₁-C₇ alkoxy substituted by substituent(s) independently selected from
 - halogen,
 - carbocyclic aryl,
- C₁-C₃ alkylcarbonyloxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by C₁-C₃ alkoxy,
- C₁-C₃ alkoxycarbonyl,
- mono- or di-C₁-C₃ alkylaminocarbonyl,
- mono- or di-C₁-C₃ alkylaminocarbonyl substituted by carbocyclic aryl,
- mono- or di-carbocyclic arylaminocarbonyl,
- mono- or di-carbocyclic arylaminocarbonyl substituted by C₁-C₃ alkyl,
- amino,
- mono- or di-C₁-C₃ alkylamino,

- C₁-C₃ alkynylcarbonylamino,
- C₁-C₃ alkynylcarbonylamino substituted by carbocyclic aryl,
- carbocyclic arylsulfonylamino,
- carbocyclic arylsulfonylamino substituted by C₁-C₃ alkyl,
- (carbocyclic aryl)NHC(O)NH,
- (carbocyclic aryl)NHC(O)NH substituted by C₁-C₃ alkoxy,
- (carbocyclic aryl)NHC(O)NH substituted by halogenated C₁-C₃ alkoxy,
- C₁-C₃ alkylthio,
- halogenated C₁-C₃ alkylthio,
- carbocyclic arylthio,
- carbocyclic arylthio substituted by cyano,
- C₁-C₃ alkylsulfonyl,
- mono- or di-C₁-C₃ alkylaminosulfonyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - C₁-C₇ alkyl,
 - halogenated C₁-C₇ alkyl,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
- (vi) heterocyclyl,
 - or heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - oxo,
 - C₁-C₃ alkylthio,
 - C₁-C₃ alkylthio substituted by carbocyclic aryl,

- C₁-C₃ alkylthio substituted by halogenated carbocyclic aryl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- heterocyclyl,
- C₁-C₃ alkoxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- C₁-C₃ alkylthio,
- C₁-C₃ alkenylthio,
- carbocyclic arylthio,
- C₁-C₃ alkylsulfonyl,
- carbocyclic arylsulfonyl,
- halogenated carbocyclic arylsulfonyl,
- carbocyclic arylsulfonyl substituted by C₁-C₄ alkyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
- halogen,
- nitro,
- C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl;

R₂ is -NHNH₂, -NHNHBoc, -N(R_{2a})(R_{2b}), morpholino, 4-acetyl-piperazyl, or 4-phenyl-piperazyl;

wherein R_{2a} is H or C₁-C₃ alkyl;

R_{2b} is C₁-C₄ alkyl, C₁-C₄ alkyl substituted by substituent(s) independently selected from

- hydroxy,
- C₁-C₃ alkoxy,

- amino,
- NHBoc,
- C₃-C₆ cycloalkyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- SO₂NH₂,
- heterocyclyl,

C₃-C₆ cycloalkyl, carbocyclic aryl, carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,
- C₁-C₃ alkyl,
- C₁-C₃ alkoxy,

or a group of Formula IV;

wherein Boc is carbamic acid *tert*-butyl ester and R₃ is C₁-C₃ alkyl or C₁-C₃ alkyl substituted by substituent(s) independently selected from

- carbocyclic aryl,
- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by C₁-C₃ alkoxy;

L is selected from Formula V - XIX;

wherein R₄ is H or C₁-C₃ alkyl;

R₅ is H, C₁-C₃ alkyl, or C₁-C₃ alkyl substituted by a substituted carbocyclic aryl;

Y is -C(O)-;

wherein carbocyclic aryl is phenyl, naphthyl, anthranyl, or biphenyl;

carbocyclyl is 10,11-dihydro-5-oxo-dibenzo[a,d]cycloheptyl, 1-oxo-indanyl, 9*H*-fluorenyl, 9-oxo-fluorenyl, acenaphthyl, anthraquinonyl, *C*-fluoren-9-ylidene, indanyl, indenyl, 1,2,3,4-tetrahydro-naphthyl, or bicyclo[2.2.1]hepteny;

heterocyclyl is 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,2-dihydro-3-oxo-pyrazolyl, 1,3-dioxo-isindolyl, 1*H*-indolyl, 1*H*-pyrrolyl, 1-oxo-3*H*-isobenzofuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2,3-dihydro-benzofuryl, 2,4-dihydro-3-oxo-pyrazolyl, 2*H*-

benzopyranyl, 2-oxo-benzopyranyl, 2-oxo-pyrrolidinyl, 3,4-dihydro-2*H*-benzo[b][1,4]dioxepinyl, 4-oxo-1,5,6,7-tetrahydro-indolyl, 4-oxo-3,4-dihydro-phthalazinyl, 4-oxo-benzopyranyl, 9,10,10-trioxo-thioxanthenyl, 9*H*-xanthenyl, azetidiny, benzimidazolyl, benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[b]thienyl, cinnolyl, furyl, imidazolyl, isoxazolyl, morpholino, morpholinyl, oxazolyl, oxolanyl, piperidyl, piridyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolidyl, quinolyl, quinoxalyl, thiazolidyl, thiazolyl, thienyl, thiolanyl, tetrahydro-thienyl, benzofuranyl, or benzothiazolyl;

halogen is fluoro, chloro, bromo, or iodo.

Other preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₀ alkyl,

C₁-C₁₀ alkyl substituted by substituent(s) independently selected from

- oxo,
- di-propylaminocarbonyl,
- methoxy substituted by carbocyclic aryl,
- methylcarbonyloxy,
- carbocyclic aryloxy,
- halogenated carbocyclic aryloxy,
- carbocyclic aryloxy substituted by nitro,
- heterocyclyloxy substituted by methyl,
- substituted heterocyclyl-ethylideneaminooxy,
- tert*-butoxycarbonylamino,
- carbocyclic arylcarbonylamino,
- C₁-C₂ alkylthio,
- C₁-C₂ alkylthio substituted by substituent(s) independently selected from
- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by methoxy,
- carbocyclic arylthio,
- heterocyclylthio substituted by nitro,

- heterocyclylthio substituted by methyl,
- C₅-C₆ cycloalkyl,
- C₅-C₆ cycloalkenyl,
- carbocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - methyl,
 - methoxy,
 - ethenyl substituted by carbocyclic aryl substituted methylsulfinyl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - oxo,
 - carbocyclic aryl,
 - heterocyclyl,
 - C₁-C₄ alkoxy,
 - halogenated C₁-C₄ alkoxy,
 - C₁-C₄ alkoxy substituted by carbocyclic aryl,
 - carbocyclic aryloxy,
 - halogenated mono-carbocyclic arylaminocarbonyl,
 - carbocyclic aryl,
 - heterocyclyl,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₂ alkyl,
 - C₁-C₂ substituted by carbocyclic aryl,
 - methoxy,
 - methoxy substituted by carbocyclic aryl,
 - carbocyclic aryl,

- halogenated carbocyclic aryl,
- (ii) C₂-C₃ alkenyl substituted by substituent(s) independently selected from
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
 - carbocyclic aryl substituted by nitro,
- (iii) C₃-C₆ cycloalkyl,
C₃-C₆ cycloalkyl substituted by substituent(s) independently selected from
 - methyl substituted by oxo,
 - methyl substituted by carbocyclic aryl,
 - carbocyclic aryl,
- (iv) carbocyclyl,
- (v) carbocyclic aryl,
carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - nitro,
 - C₁-C₉ alkyl,
 - C₁-C₉ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - oxo,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by methyl,
 - carbocyclic aryloxy,
 - C₁-C₇ alkoxy,
 - halogenated C₁-C₇ alkoxy,
 - C₁-C₇ alkoxy substituted by carbocyclic aryl,
 - methylcarbonyloxy,
 - carbocyclic aryloxy,
 - carbocyclic aryloxy substituted by methoxy,
 - amino,
 - di-methylamino,

- propargynylcarbonylamino substituted by carbocyclic aryl,
- carbocyclic arylsulfonylamino substituted by methyl,
- (carbocyclic aryl)NHC(O)NH substituted by halogenated methoxy,
- halogenated methylthio,
- carbocyclic arylthio substituted by cyano,
- di-propylamino sulfonyl,
- mono- or di- ethylaminocarbonyl substituted by carbocyclic aryl,
- carbocyclic aryl,
- heterocyclyl substituted by methyl,
- heterocyclyl substituted by halogenated carbocyclic aryl,
- (vi) heterocyclyl,
- or heterocyclyl substituted by substituent(s) independently selected from
- halogen,
- nitro,
- C₁-C₄ alkyl,
- C₁-C₄ alkyl substituted by substituent(s) independently selected from
- halogen,
- methylthio substituted by halogenated carbocyclic aryl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- heterocyclyl,
- methoxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by methyl,
- C₁-C₃ alkylthio,
- propenylthio,
- carbocyclic arylthio,
- C₁-C₃ alkylsulfonyl,
- carbocyclic arylsulfonyl substituted by C₁-C₄ alkyl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by methyl,

- carbocyclic aryl substituted by nitro,

- heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula Va, VIIIa, or IXa;

wherein R₄ and R₅ are independently selected from H or C₁-C₃ alkyl;

Y is -C(O)-;

wherein carbocyclic aryl is phenyl, naphthyl, anthranyl, or biphenyl;

carbocyclyl is 1-oxo-indanyl, 9-oxo-fluorenyl, indenyl, anthraquinonyl, C-fluoren-9-ylidene, 1,2,3,4-tetrahydro-naphthyl, or bicyclo[2.2.1]hepteny;

heterocyclyl is 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,2-dihydro-3-oxo-pyrazolyl, 1,3-dioxo-isoindolyl, 1*H*-indolyl, 1*H*-pyrrolyl, 1-oxo-3*H*-isobenzofuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2,4-dihydro-3-oxo-pyrazolyl, 2*H*-benzopyranyl, 2-oxo-benzopyranyl, 3,4-dihydro-2*H*-benzo[b][1,4]dioxepinyl, 4-oxo-3,4-dihydro-phthalazinyl, 4-oxo-benzopyranyl, 9,10,10-trioxo-thioxanthenyl, 9*H*-xanthenyl, azetidiny, benzimidazolyl, benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[b]thienyl, furyl, imidazolyl, isoxazolyl, morpholino, morpholinyl, oxolanyl, piperidyl, piridyl, pyrazolyl, pyridyl, quinolyl, quinoxalyl, thiazolidyl, thiazolyl, thienyl, thiolanyl, 2,3-dihydro-1-oxo-isoindolyl, 2,3-dihydro-benzofuryl, 2-oxo-pyrrolidinyl, 4-oxo-1,5,6,7-tetrahydro-indolyl, cinnolyl, pyrimidyl, pyrrolidyl, tetrahydro-thienyl, benzofuranyl, or benzothiazolyl;

halogen is fluoro, chloro, bromo, or iodo.

Other more preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₀ alkyl substituted by substituent(s) independently selected from

- oxo,
- di-propylaminocarbonyl,
- methoxy substituted by carbocyclic aryl,
- methylcarbonyloxy,
- carbocyclic aryloxy,
- halogenated carbocyclic aryloxy,

- carbocyclic aryloxy substituted by nitro,
- heterocyclyloxy substituted by methyl,
- tert*-butoxycarbonylamino,
- carbocyclic arylcarbonylamino,
- C₁-C₂ alkylthio,
- C₁-C₂ alkylthio substituted by substituent(s) independently selected from
 - halogenated carbocyclic aryl,
 - carbocyclic aryl substituted by methoxy,
 - carbocyclic arylthio,
 - heterocyclylthio substituted by nitro,
 - heterocyclylthio substituted by methyl,
 - C₅-C₆ cycloalkenyl,
 - carbocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - methyl,
 - methoxy,
 - ethenyl substituted by carbocyclic aryl substituted methylsulfinyl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - oxo,
 - carbocyclic aryl,
 - heterocyclyl,
 - C₁-C₄ alkoxy,
 - halogenated C₁-C₄ alkoxy,
 - C₁-C₄ alkoxy substituted by carbocyclic aryl,
 - carbocyclic aryloxy,
 - halogenated mono-carbocyclic arylaminocarbonyl,
 - carbocyclic aryl,

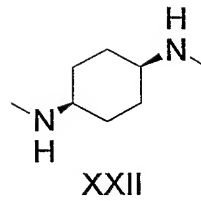
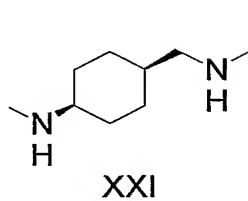
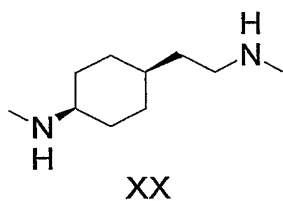
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₂ alkyl,
 - C₁-C₂ substituted by carbocyclic aryl,
 - methoxy,
 - methoxy substituted by carbocyclic aryl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
- (ii) C₂-C₃ alkenyl substituted by substituent(s) independently selected from
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
 - carbocyclic aryl substituted by nitro,
- (iii) C₃-C₆ cycloalkyl substituted by substituent(s) independently selected from
 - methyl substituted by oxo,
 - methyl substituted by carbocyclic aryl,
 - carbocyclic aryl,
- (iv) carbocyclyl,
- (v) carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - nitro,
 - C₁-C₉ alkyl,
 - C₁-C₉ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - oxo,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by methyl,
 - carbocyclic aryloxy,
 - C₁-C₇ alkoxy,
 - halogenated C₁-C₇ alkoxy,
 - C₁-C₇ alkoxy substituted by carbocyclic aryl,

- methylcarbonyloxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by methoxy,
- amino,
- di-methylamino,
- propargynylcarbonylamino substituted by carbocyclic aryl,
- carbocyclic arylsulfonylamino substituted by methyl,
- (carbocyclic aryl)NHC(O)NH substituted by halogenated methoxy,
- halogenated methylthio,
- carbocyclic arylthio substituted by cyano,
- di-propylamino sulfonyl,
- mono- or di- ethylaminocarbonyl substituted by carbocyclic aryl,
- carbocyclic aryl,
- heterocyclyl substituted by methyl,
- heterocyclyl substituted by halogenated carbocyclic aryl,
- (vi) or heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - methylthio substituted by halogenated carbocyclic aryl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
 - heterocyclyl,
 - methoxy,
 - carbocyclic aryloxy,
 - carbocyclic aryloxy substituted by methyl,
 - C₁-C₃ alkylthio,
 - propenylthio,
 - carbocyclic arylthio,
 - C₁-C₃ alkylsulfonyl,

- carbocyclic arylsulfonyl,
- carbocyclic arylsulfonyl substituted by C₁-C₄ alkyl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by methyl,
- carbocyclic aryl substituted by nitro,
- heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula XX - XXII;



Y is -C(O)-;

wherein carbocyclic aryl is phenyl, naphthyl, or biphenyl;

carbocyclyl is 1-oxo-indanyl, 9-oxo-fluorenyl, indenyl, anthraquinonyl, C-fluoren-9-ylidene, 1,2,3,4-tetrahydro-naphthyl, or bicyclo[2.2.1]hepteny;

heterocyclyl is 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,2-dihydro-3-oxo-pyrazolyl, 1*H*-indolyl, 1*H*-pyrrolyl, 2,4-dihydro-3-oxo-pyrazolyl, 2*H*-benzopyranyl, 4-oxo-benzopyranyl, azetidiny, benzo[b]thienyl, furyl, isoxazolyl, morpholinyl, piperidyl, piridyl, pyrazolyl, pyridyl, quinolyl, thiazolidyl, thiazolyl, thienyl, thiolanyl, 2,3-dihydro-1-oxo-isoindolyl, 2,3-dihydro-benzofuryl, 2-oxo-benzopyranyl, 2-oxo-pyrrolidinyl, 4-oxo-1,5,6,7-tetrahydro-indolyl, 9*H*-xanthenyl, cinnolyl, imidazolyl, morpholino, pyrimidyl, pyrrolidyl, tetrahydro-thienyl, benzofuranyl, or benzothiazolyl;

halogen is fluoro, chloro, bromo, or iodo.

Further other more preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₅ alkyl substituted by substituent(s) independently selected from

- oxo,
- di-propylaminocarbonyl,
- methoxy substituted by carbocyclic aryl,
- methylcarbonyloxy,
- carbocyclic aryloxy,
- halogenated carbocyclic aryloxy,
- carbocyclic aryloxy substituted by nitro,
- heterocyclyloxy substituted by methyl,
- substituted heterocyclyl-ethylideneaminooxy,
- tert*-butoxycarbonylamino,
- carbocyclic arylcarbonylamino,
- C₁-C₂ alkylthio,
- C₁-C₂ alkylthio substituted by substituent(s) independently selected from
 - halogenated carbocyclic aryl,
 - carbocyclic aryl substituted by methoxy,
 - carbocyclic arylthio,
 - heterocyclylthio substituted by nitro,
 - heterocyclylthio substituted by methyl,
 - cyclohexenyl,
 - carbocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - methyl,
 - methoxy,
 - ethenyl substituted by carbocyclic aryl substituted methylsulfinyl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - oxo,

- carbocyclic aryl,
- heterocyclyl,
- C₁-C₂ alkoxy,
- halogenated C₁-C₂ alkoxy,
- C₁-C₂ alkoxy substituted by carbocyclic aryl,
- carbocyclic aryloxy,
- halogenated mono-carbocyclic arylaminocarbonyl,
- carbocyclic aryl,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₂ alkyl,
 - C₁-C₂ substituted by carbocyclic aryl,
 - methoxy,
 - methoxy substituted by carbocyclic aryl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
- (ii) C₂-C₃ alkenyl substituted by substituent(s) independently selected from
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
 - carbocyclic aryl substituted by nitro,
- (iii) C₃-C₆ cycloalkyl substituted by substituent(s) independently selected from
 - methyl substituted by oxo,
 - methyl substituted by carbocyclic aryl,
 - carbocyclic aryl,
- (iv) carbocyclyl,
- (v) carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₂ alkyl substituted by substituent(s) independently selected from

- halogen,
- oxo,
- carbocyclic aryl,
- carbocyclic aryl substituted by methyl,
- carbocyclic aryloxy,
- C₁-C₂ alkoxy,
- halogenated C₁-C₂ alkoxy,
- C₁-C₂ alkoxy substituted by carbocyclic aryl,
- methylcarbonyloxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by methoxy,
- amino,
- di-methylamino,
- propargynylcarbonylamino substituted by carbocyclic aryl,
- carbocyclic arylsulfonylamino substituted by methyl,
- (carbocyclic aryl)NHC(O)NH substituted by halogenated methoxy,
- halogenated methylthio,
- carbocyclic arylthio substituted by cyano,
- di-propylamino sulfonyl,
- mono- or di- ethylaminocarbonyl substituted by carbocyclic aryl,
- carbocyclic aryl,
- heterocyclyl substituted by methyl,
- heterocyclyl substituted by halogenated carbocyclic aryl,
- (vi) or heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - methylthio substituted by halogenated carbocyclic aryl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,

- heterocyclyl,
- methoxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by methyl,
- C₁-C₃ alkylthio,
- propenylthio,
- carbocyclic arylthio,
- C₁-C₃ alkylsulfonyl,
- carbocyclic arylsulfonyl,
- carbocyclic arylsulfonyl substituted by methyl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by methyl,
- carbocyclic aryl substituted by nitro,
- heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula XX - XXII;

Y is -C(O)-;

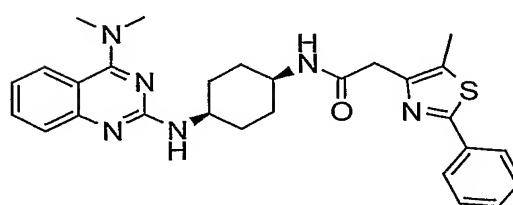
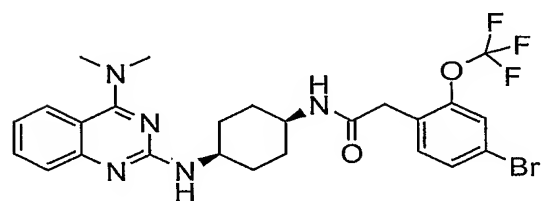
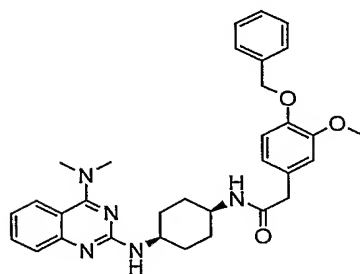
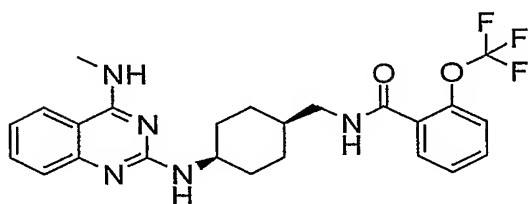
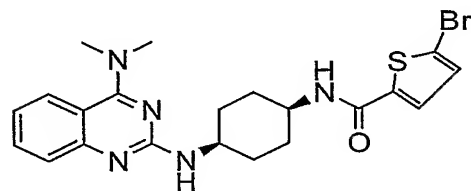
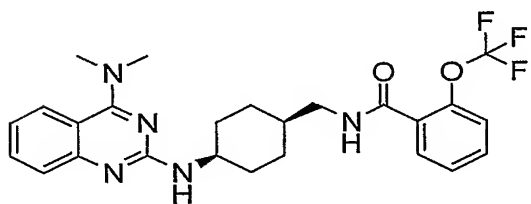
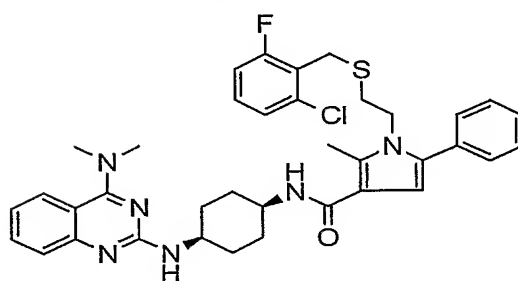
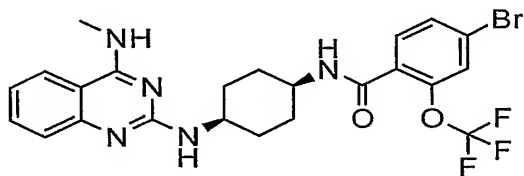
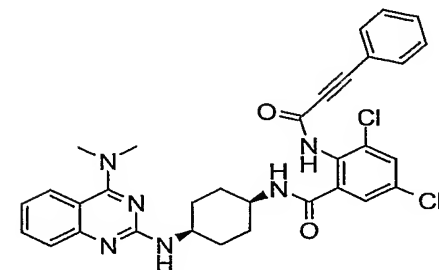
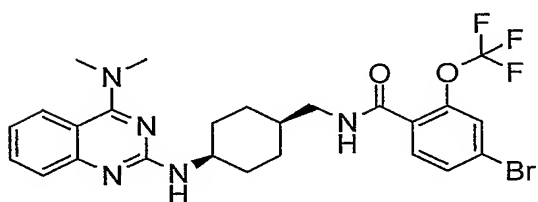
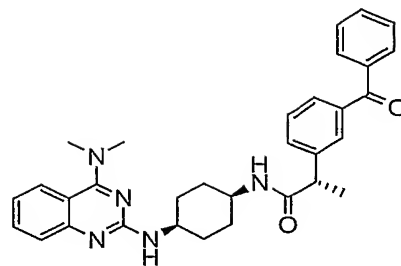
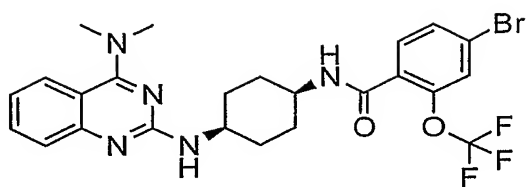
wherein carbocyclic aryl is phenyl, naphthyl, or biphenyl;

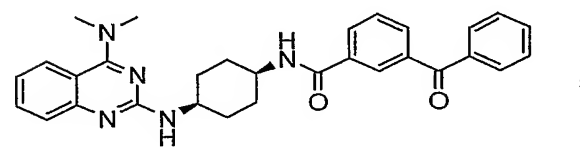
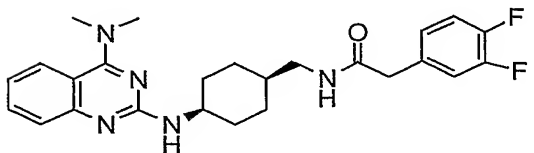
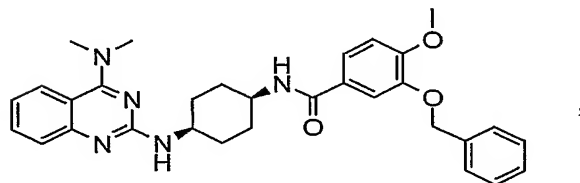
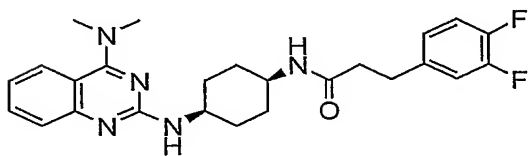
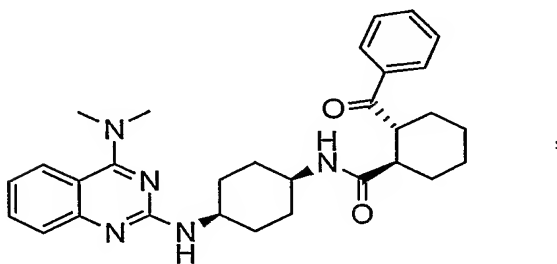
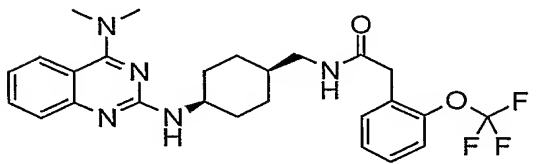
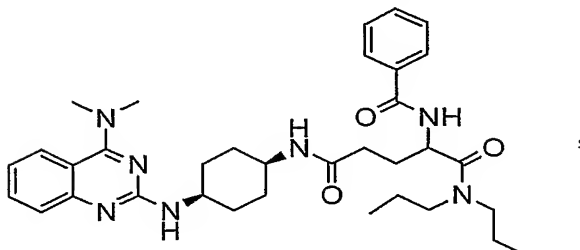
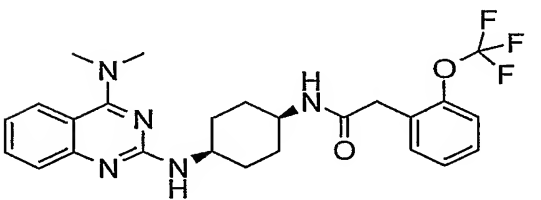
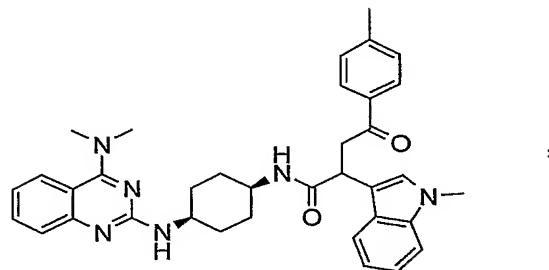
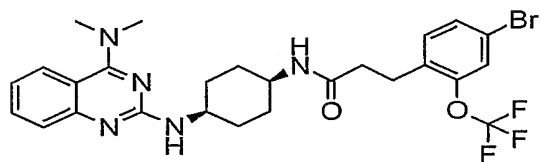
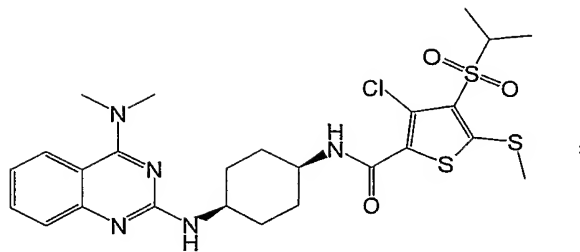
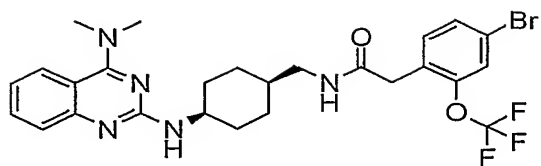
carbocyclyl is 1-oxo-indanyl, indenyl, 9-oxo-fluorenyl, 1,2,3,4-tetrahydro-naphthyl, or bicyclo[2.2.1]hepteny;

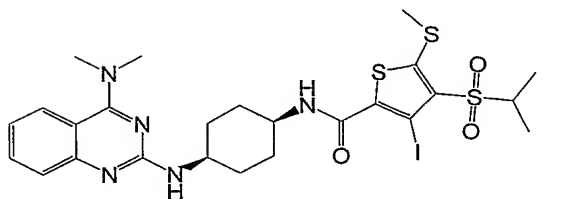
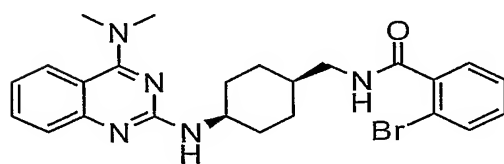
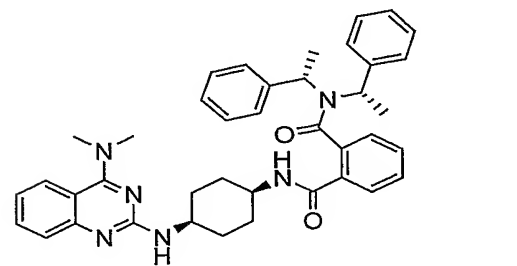
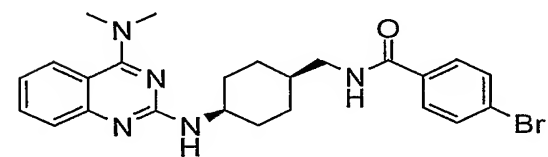
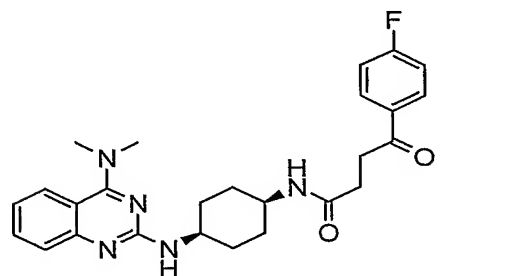
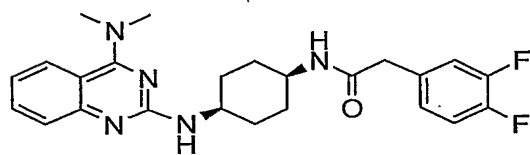
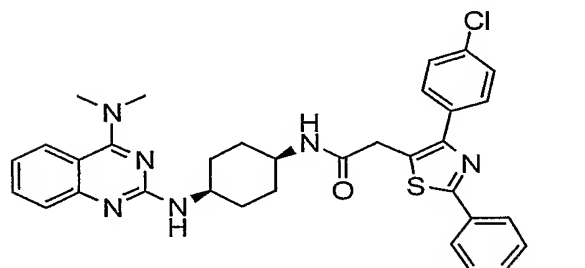
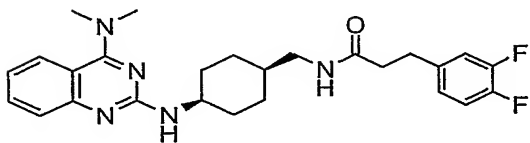
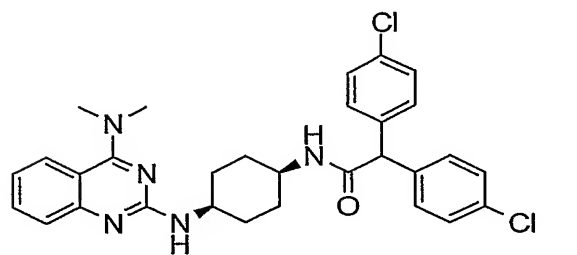
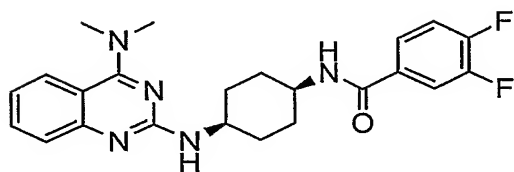
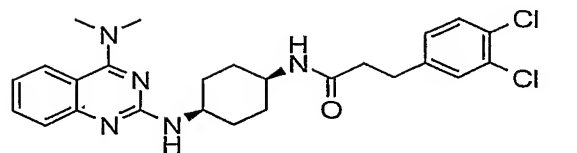
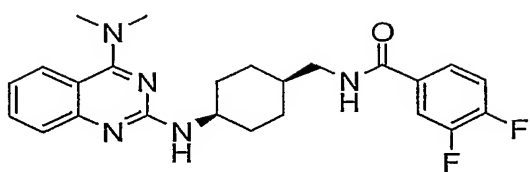
heterocyclyl is 1*H*-indolyl, 2,4-dihydro-3-oxo-pyrazolyl, furyl, pyrazolyl, pyridyl, thienyl, 1,2,3-triazolyl, 1*H*-pyrrolyl, 2,3-dihydro-1-oxo-isoindolyl, 2,3-dihydro-benzofuryl, 2*H*-benzopyranyl, 2-oxo-benzopyranyl, 4-oxo-1,5,6,7-tetrahydro-indolyl, imidazolyl, isoxazolyl, morpholino, morpholinyl, pyrazolyl, pyrimidyl, quinolyl, thiazolyl, tetrahydro-thienyl, benzofuranyl, or benzothiazolyl;

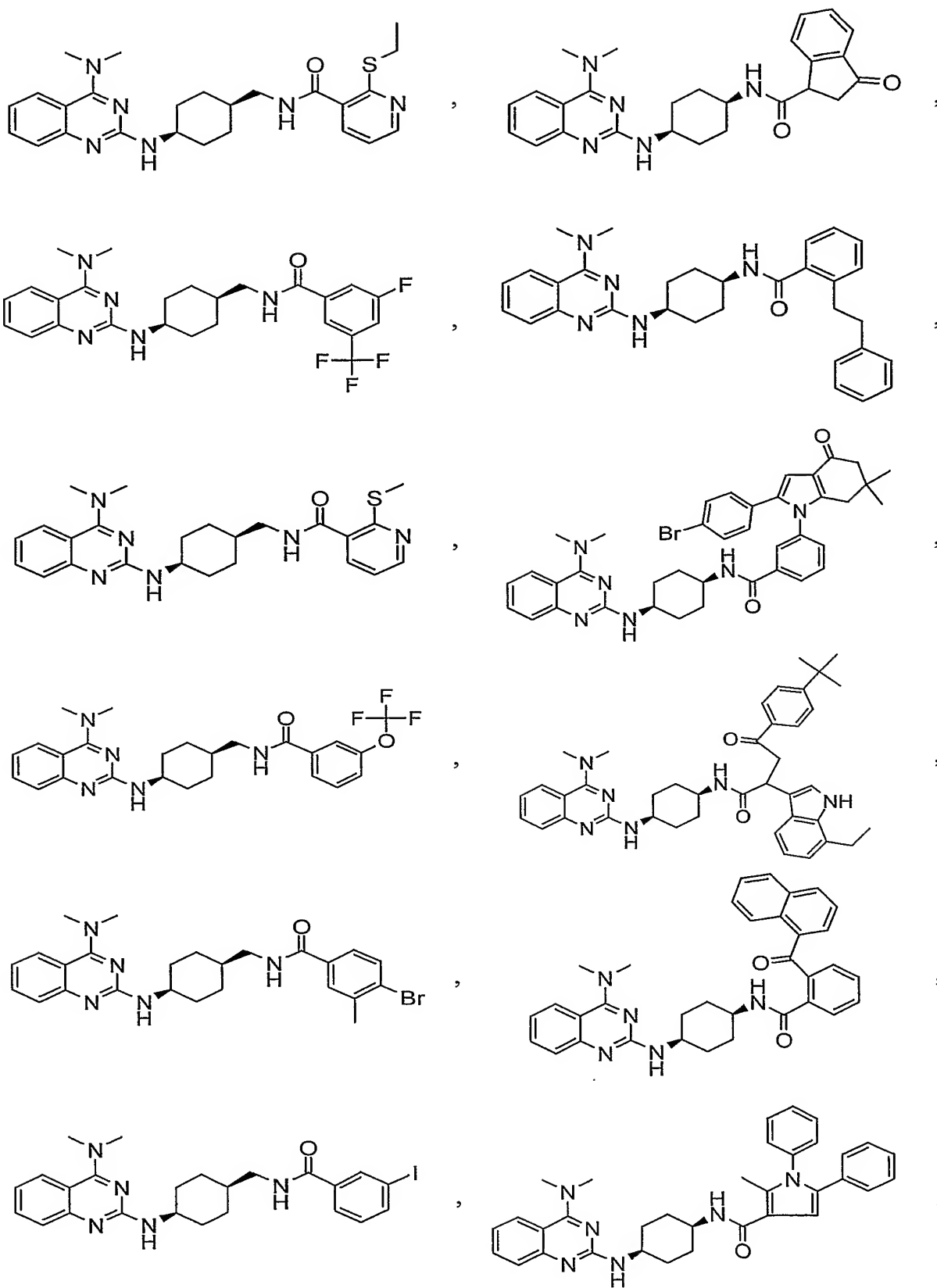
halogen is fluoro, chloro, bromo, or iodo.

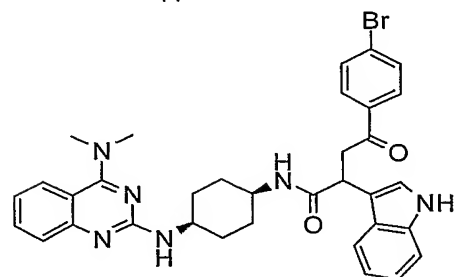
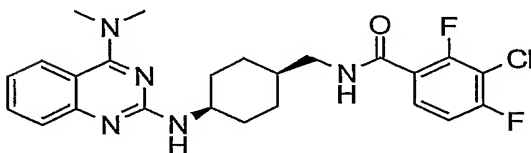
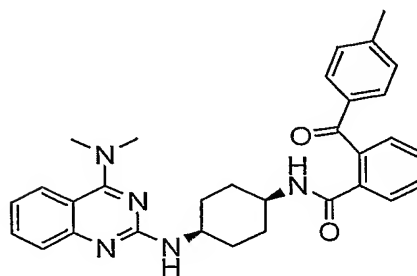
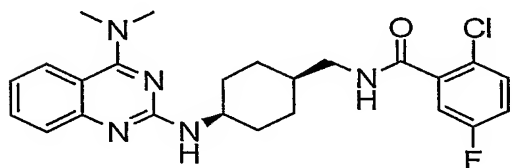
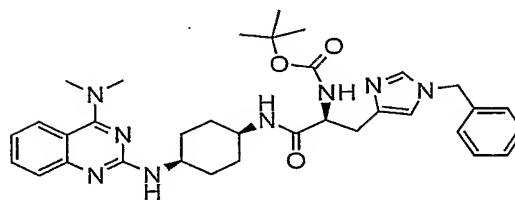
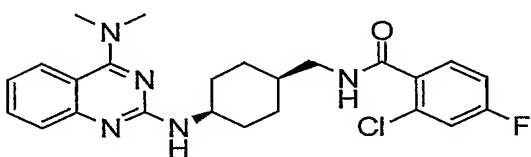
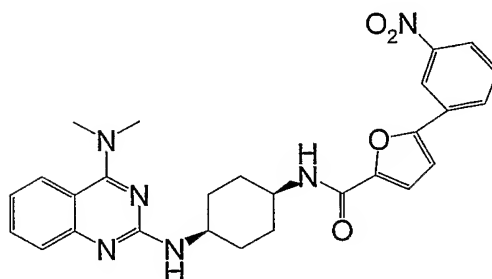
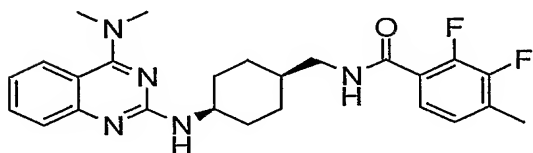
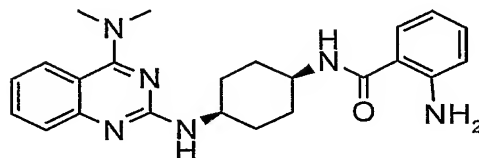
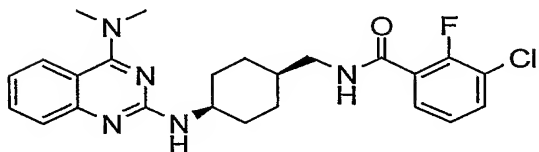
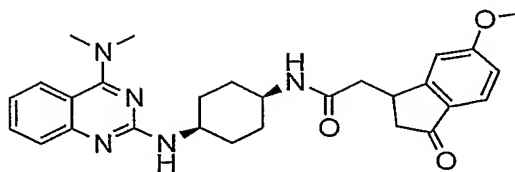
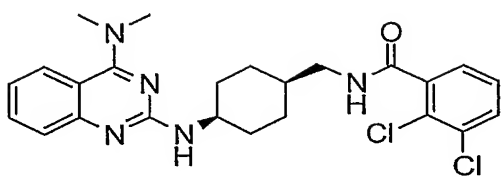
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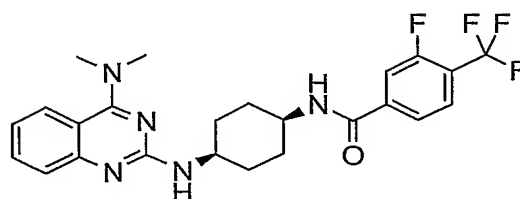
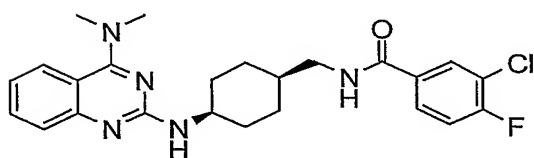
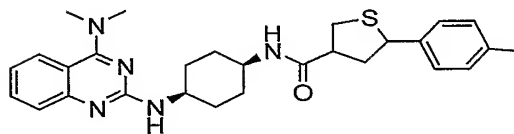
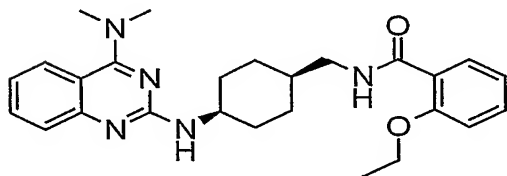
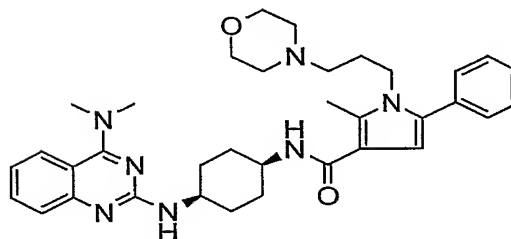
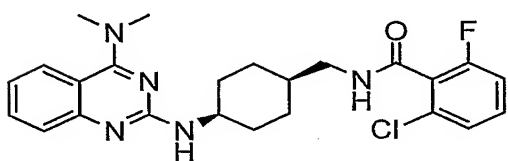
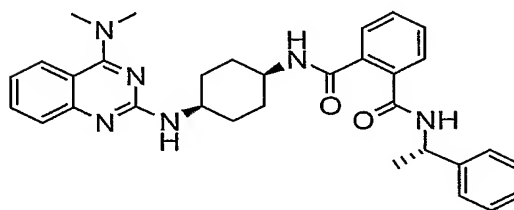
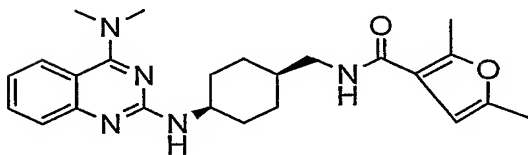
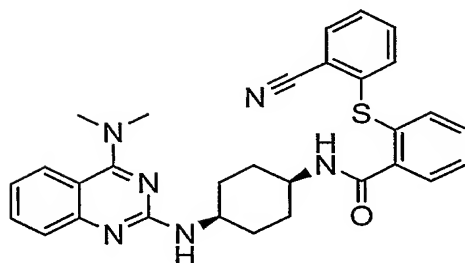
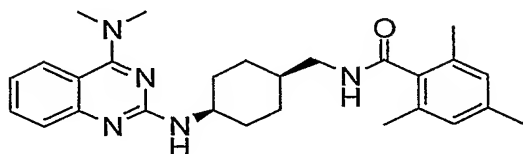
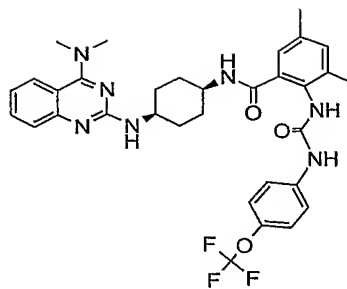


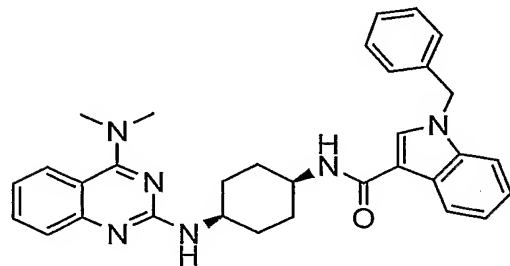
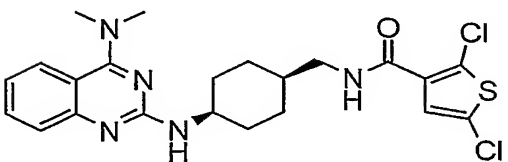
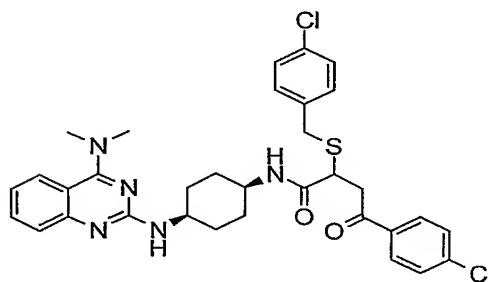
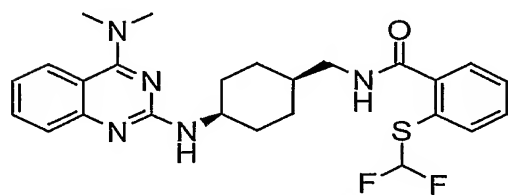
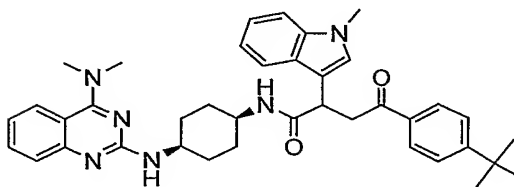
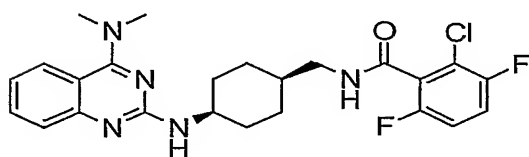
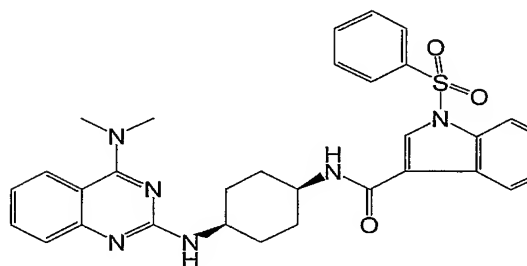
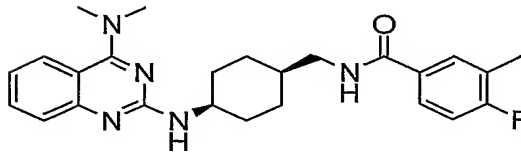
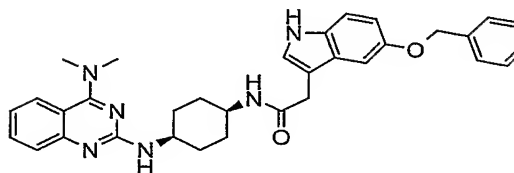
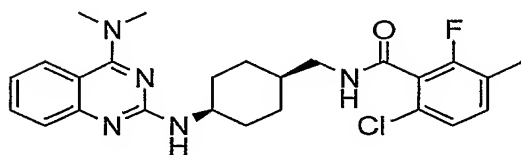
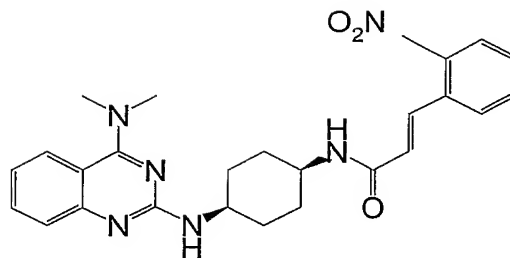
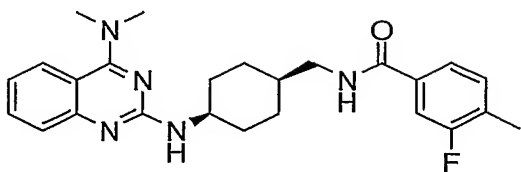


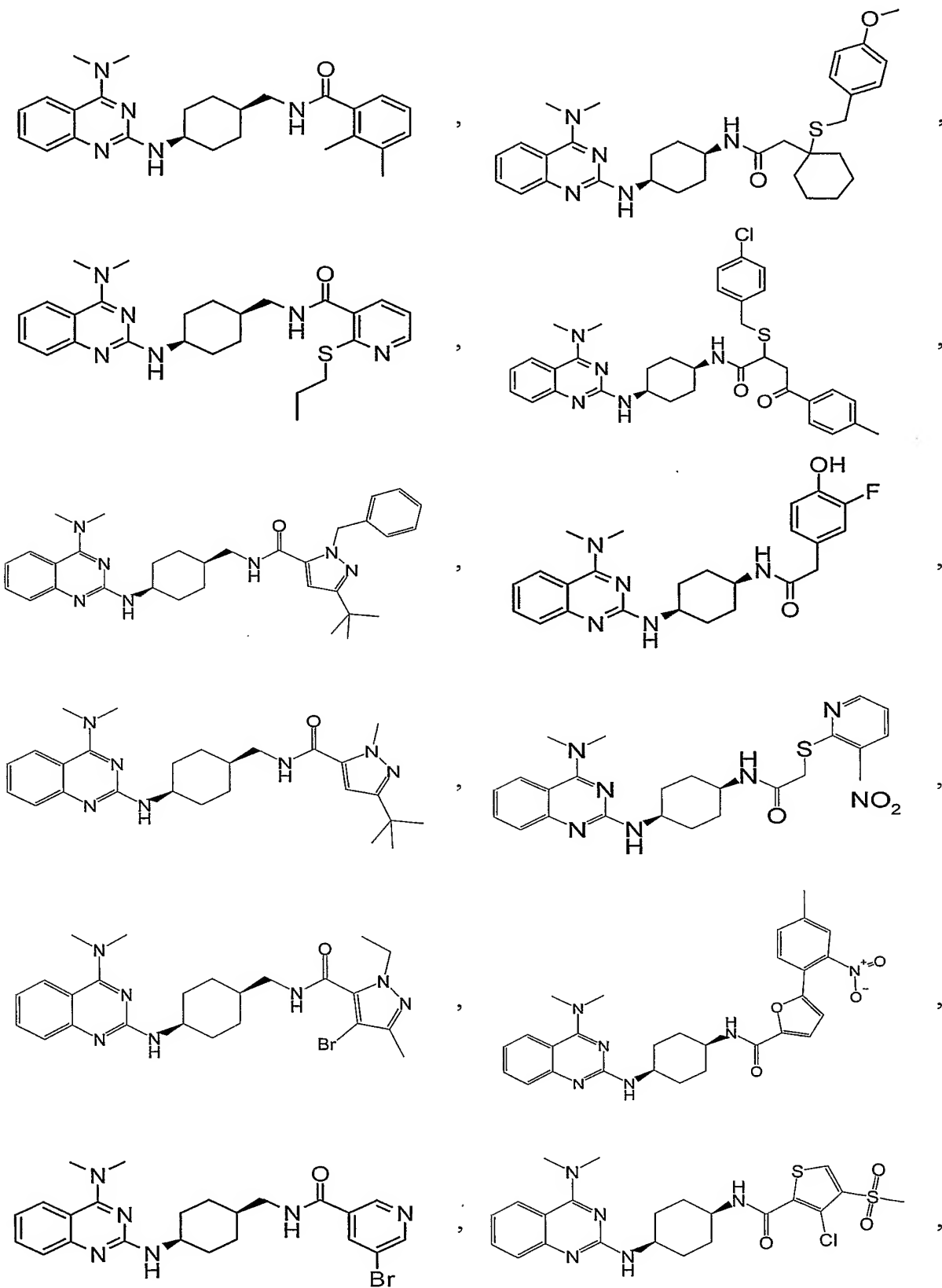


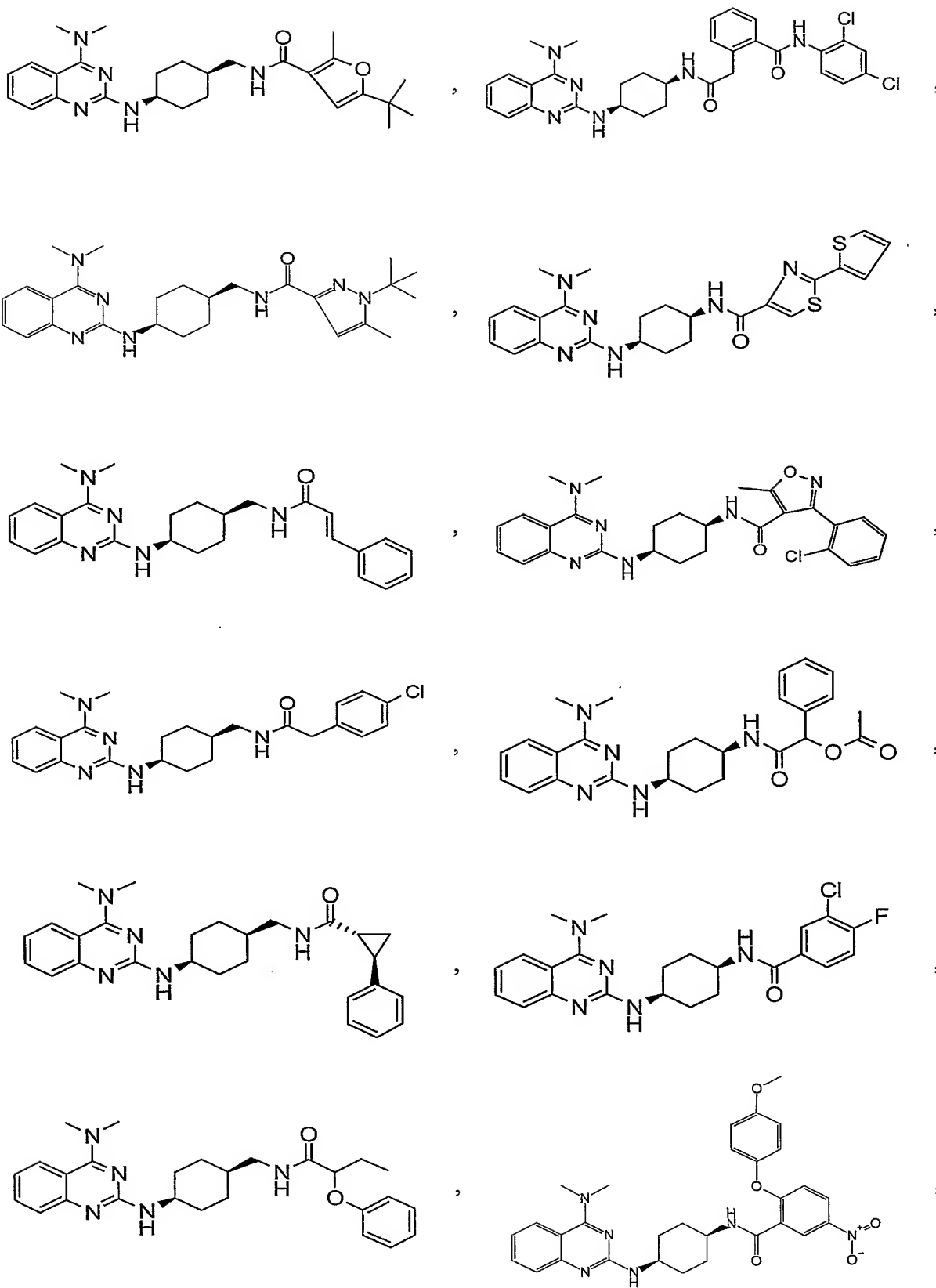


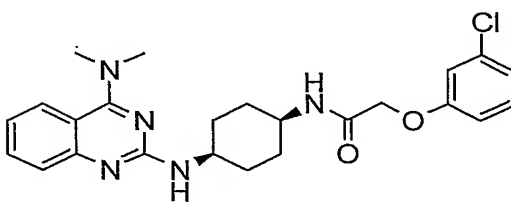
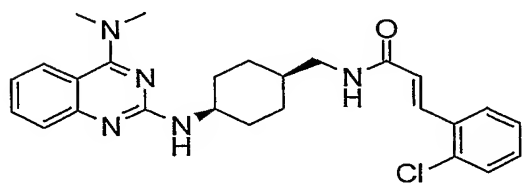
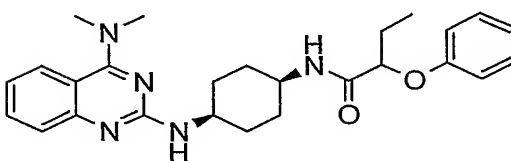
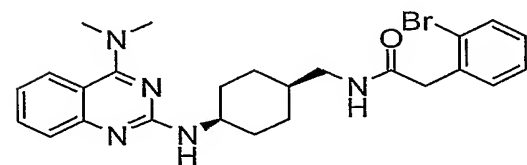
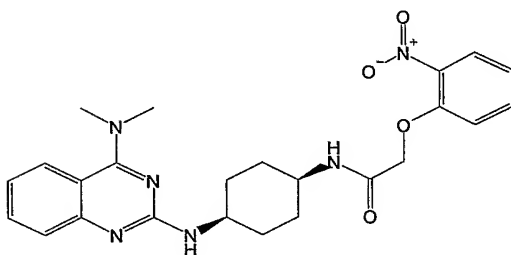
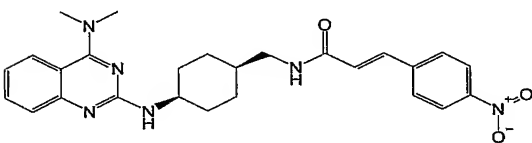
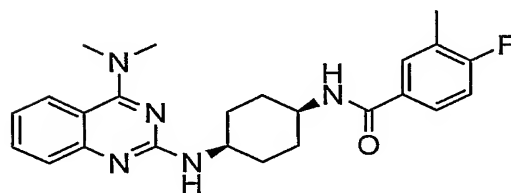
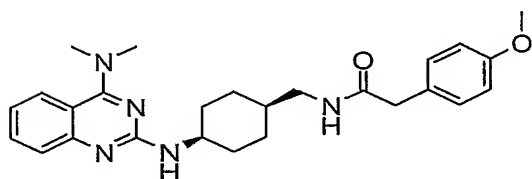
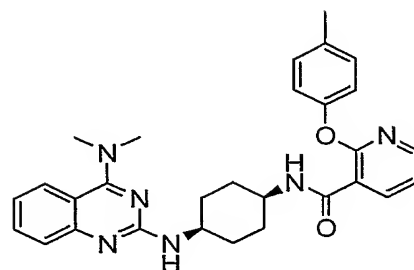
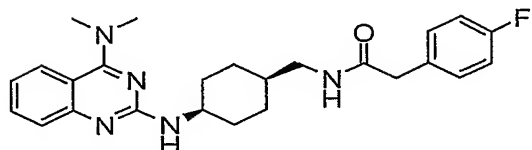
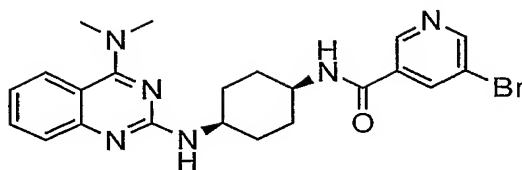
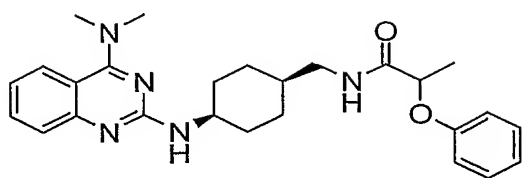


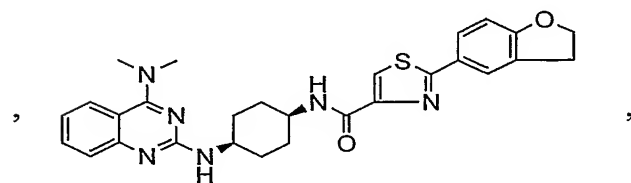
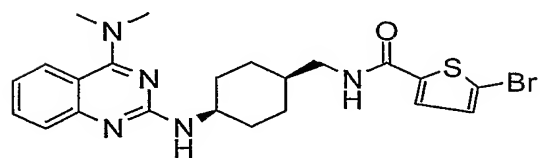
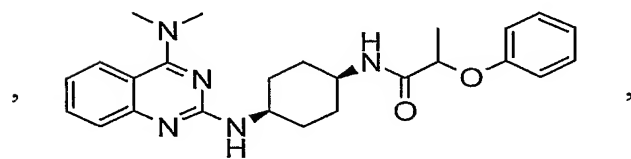
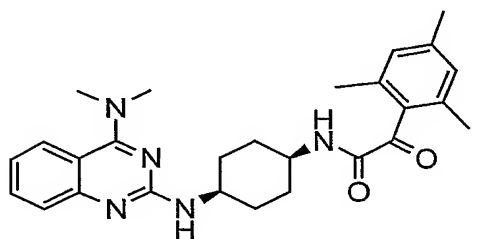
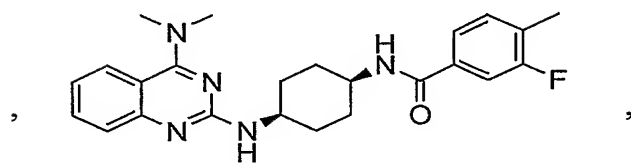
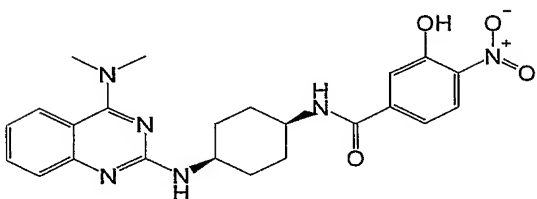
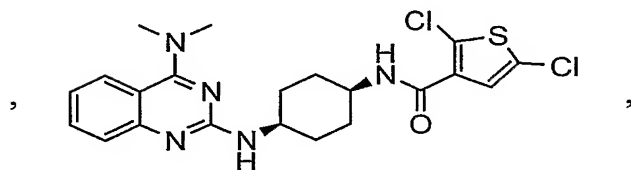
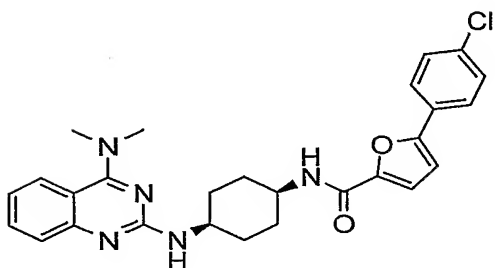
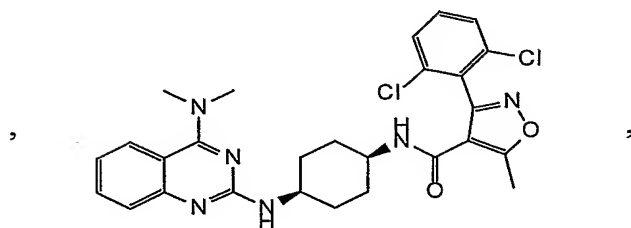
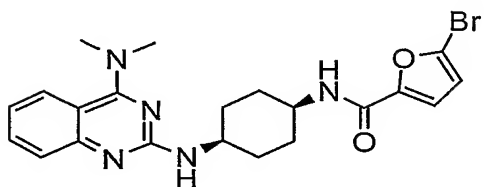
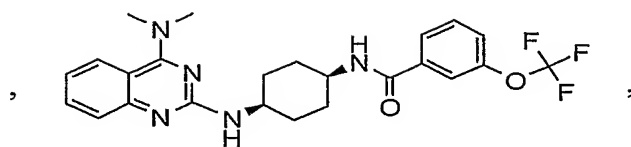
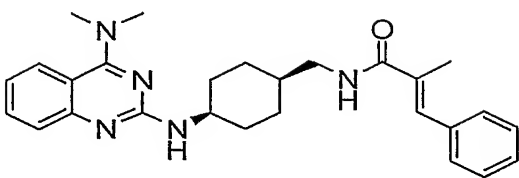


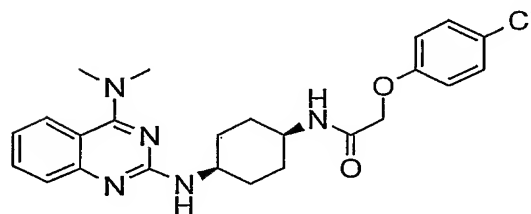
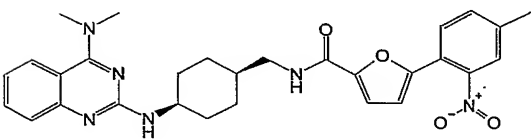
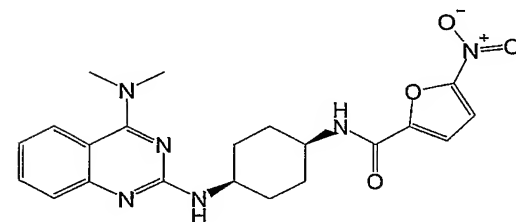
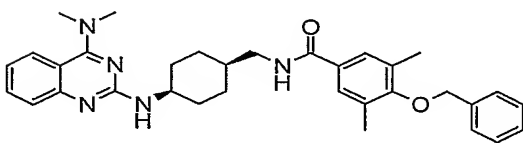
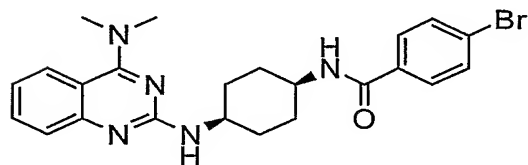
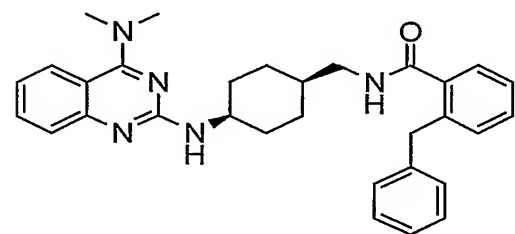
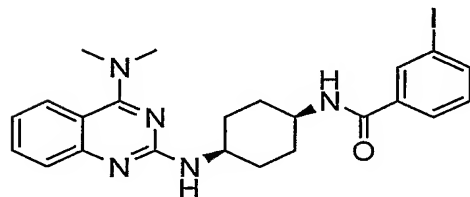
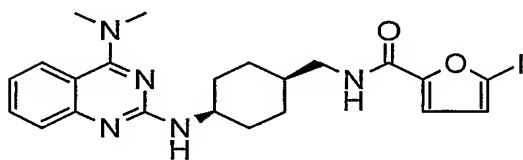
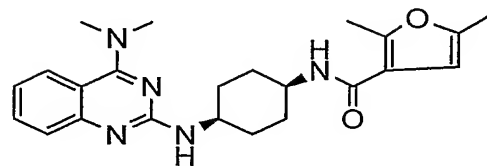
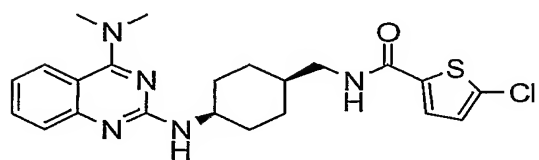
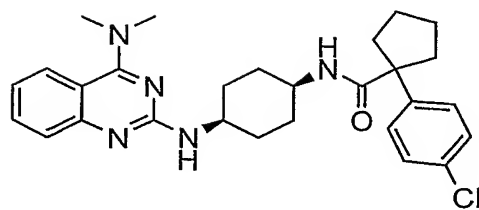
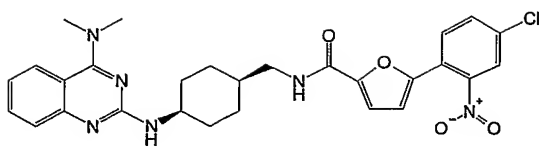


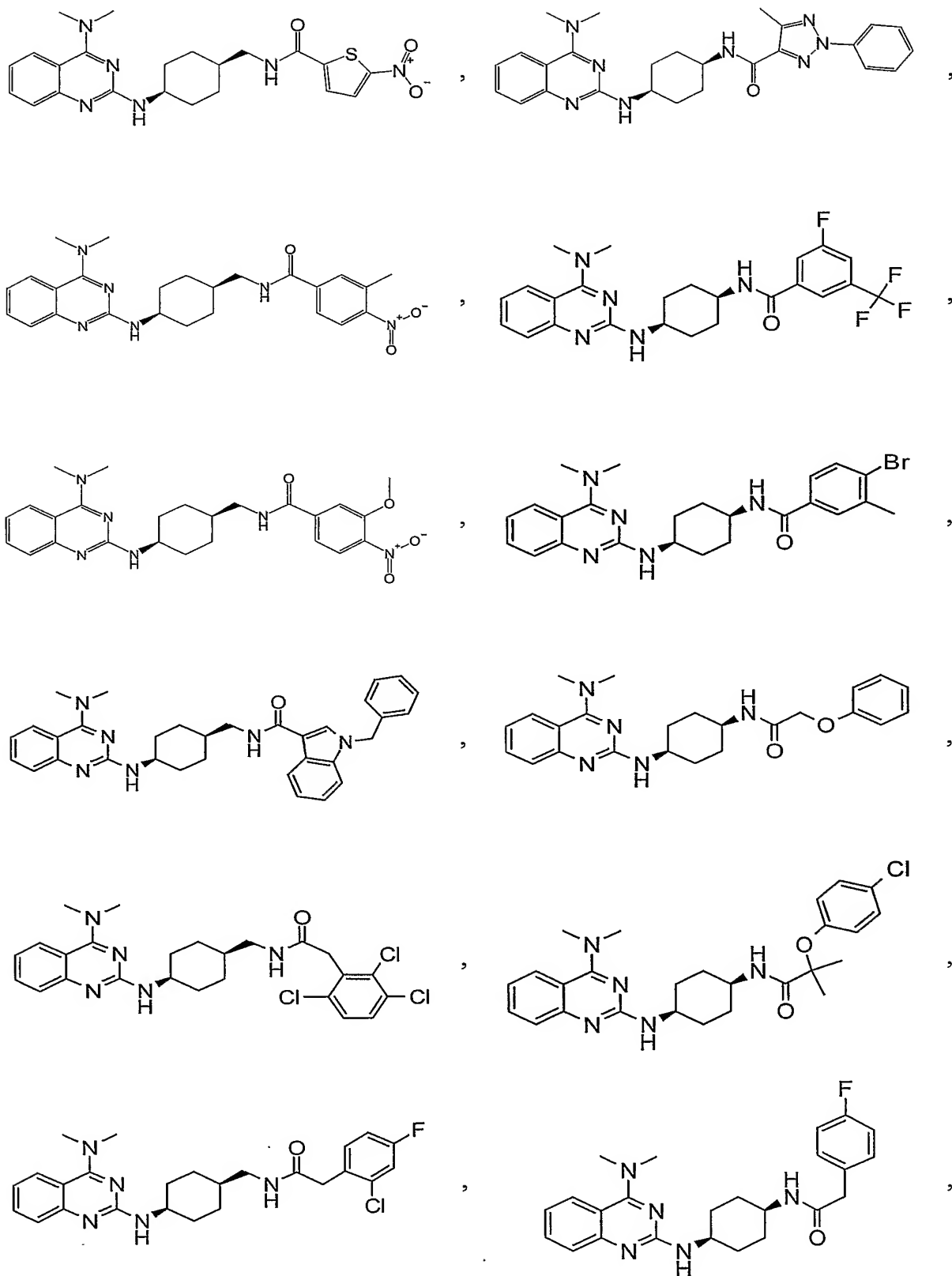


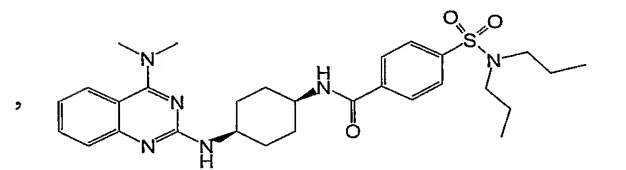
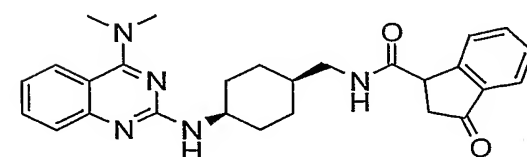
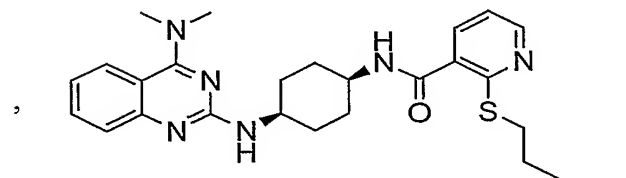
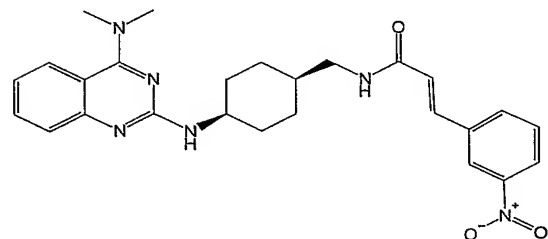
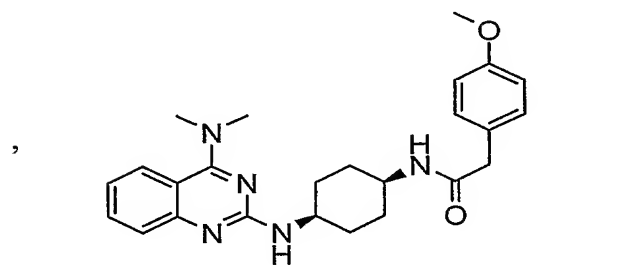
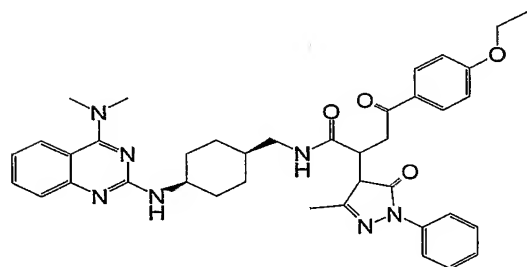
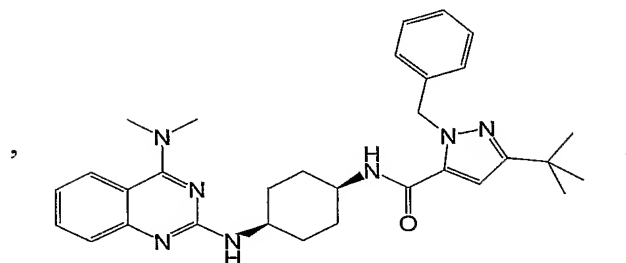
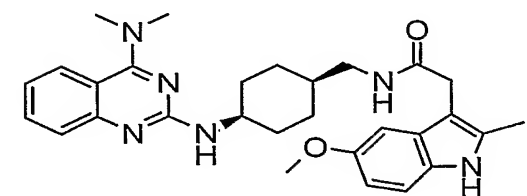
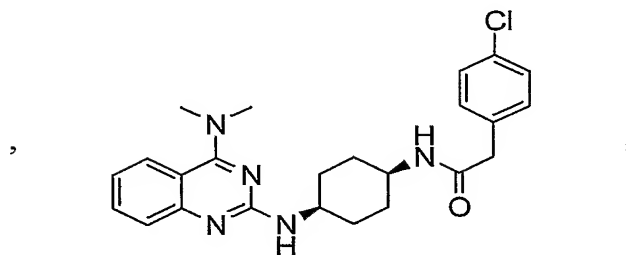
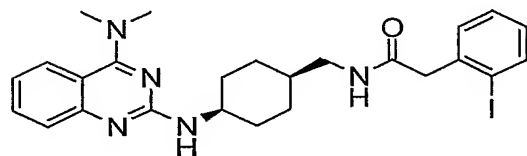
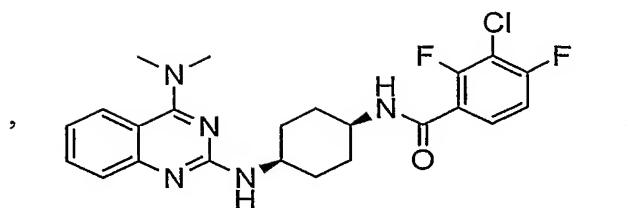
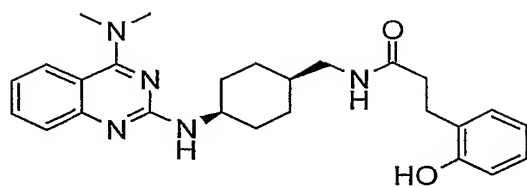


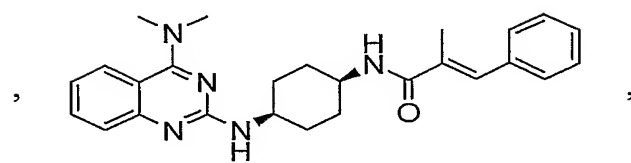
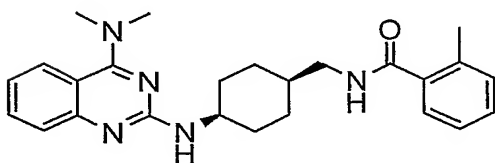
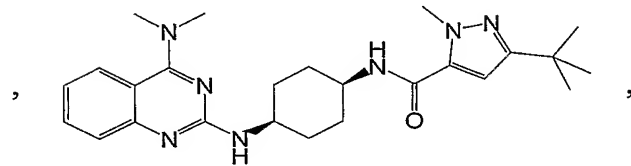
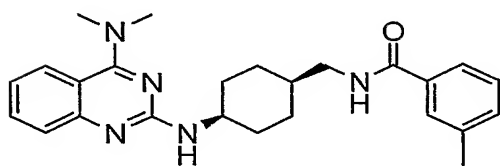
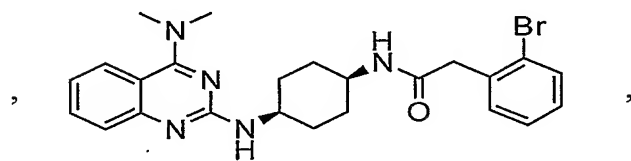
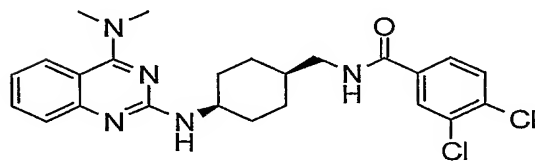
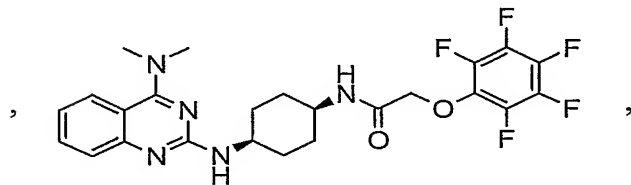
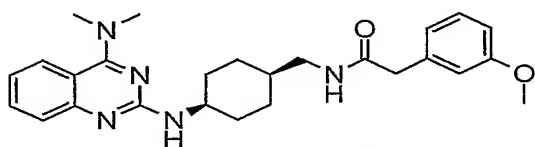
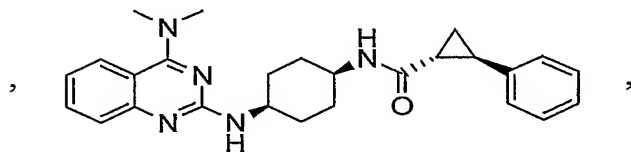
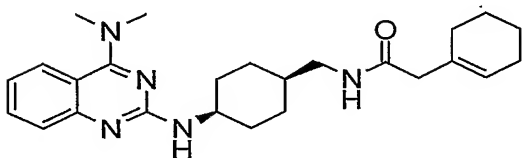
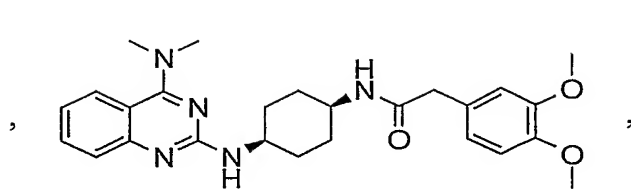
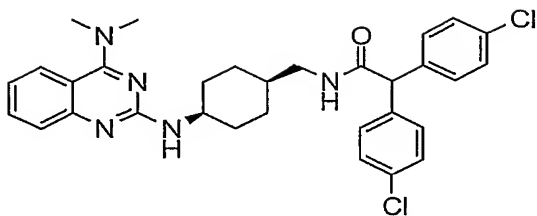


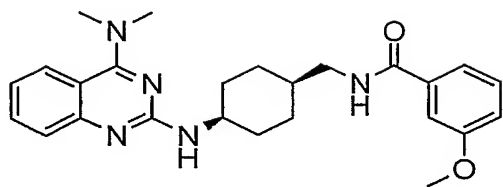




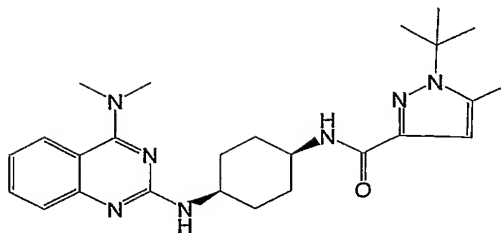




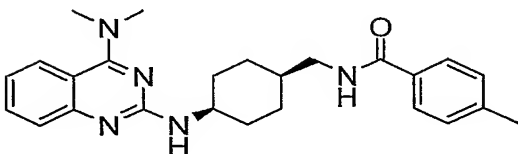




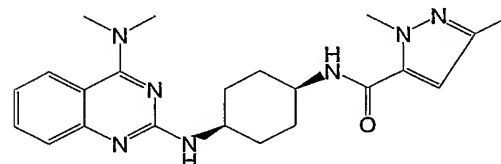
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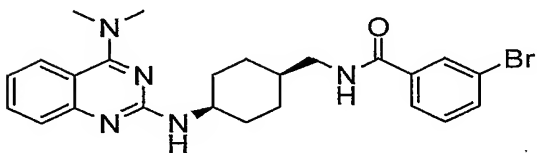
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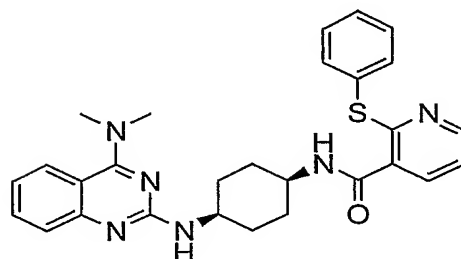
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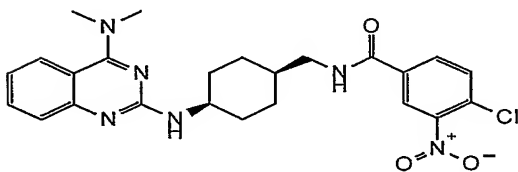
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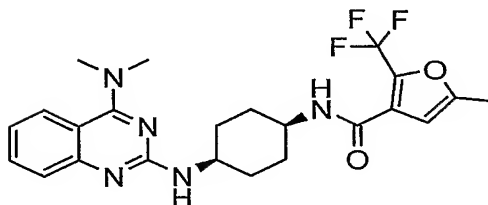
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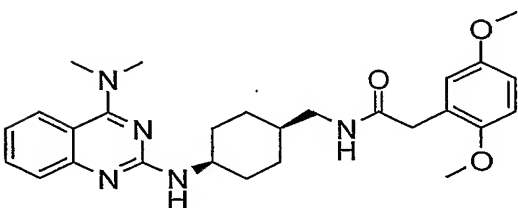
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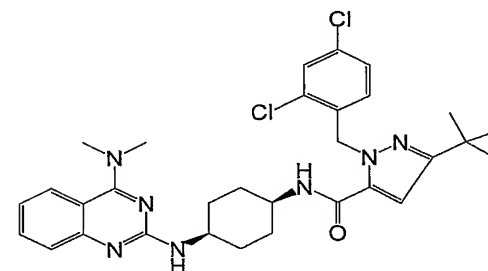
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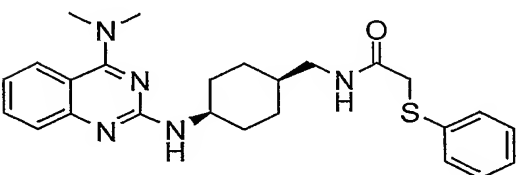
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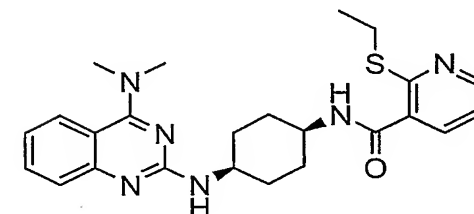
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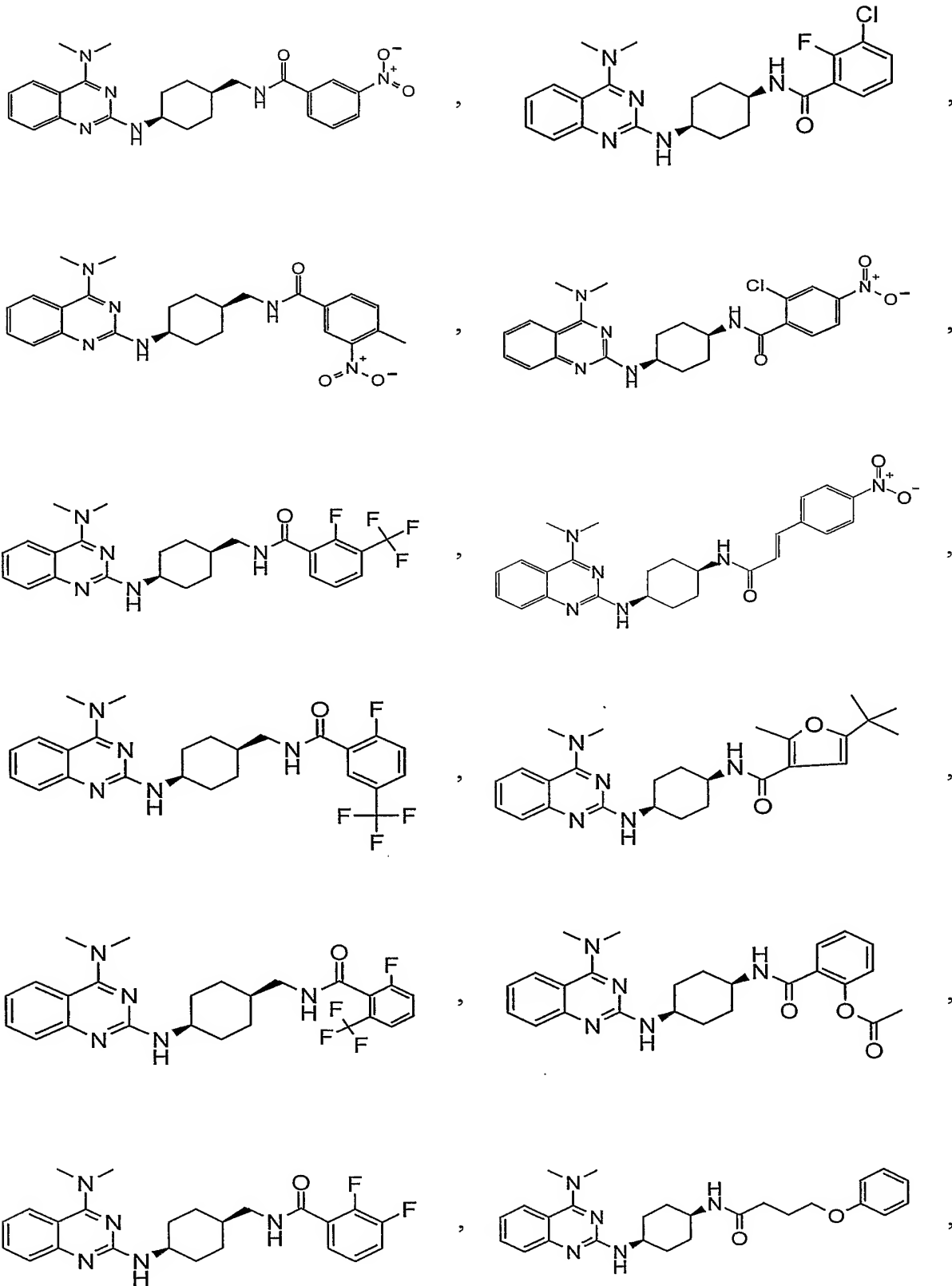
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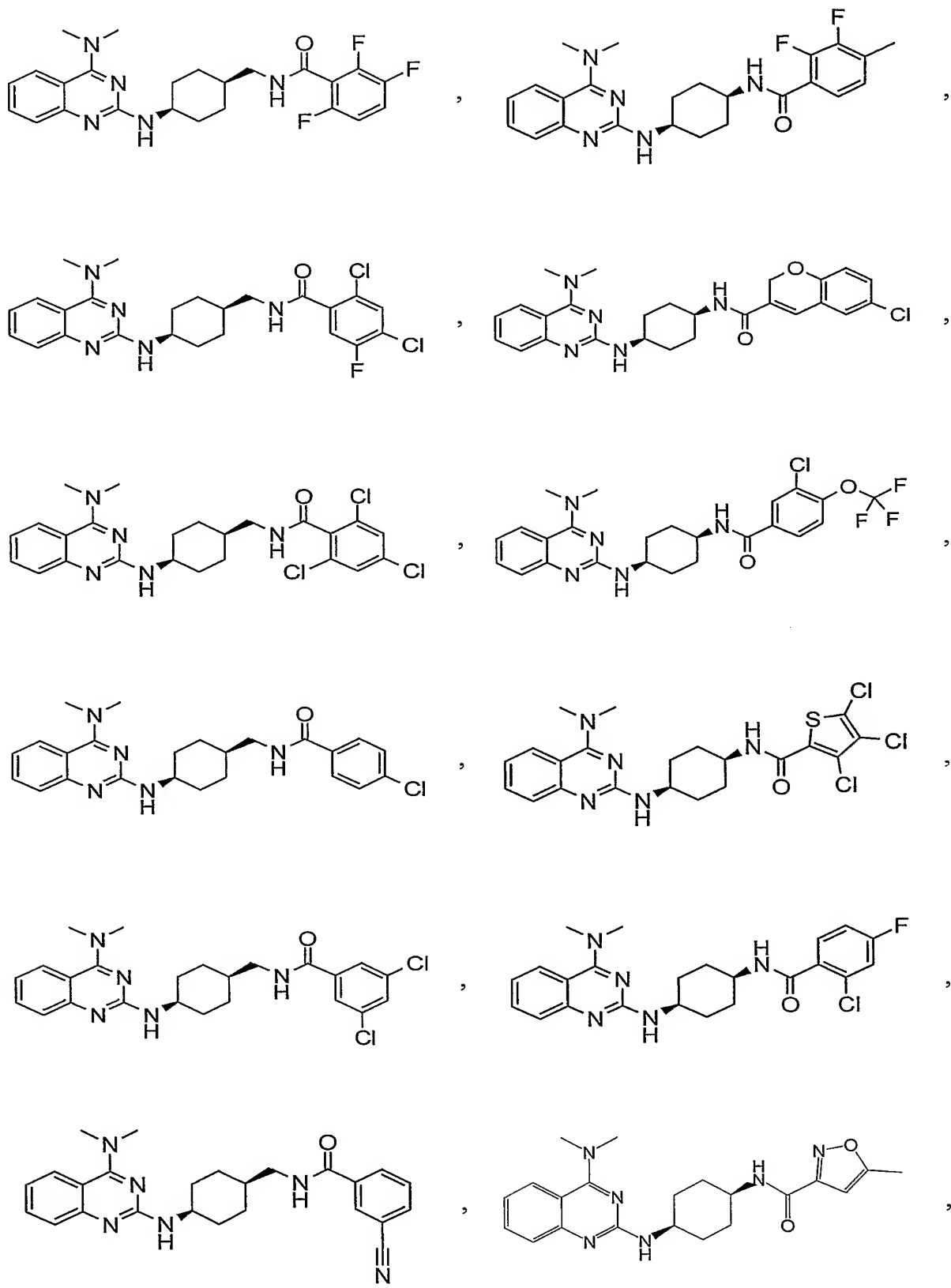


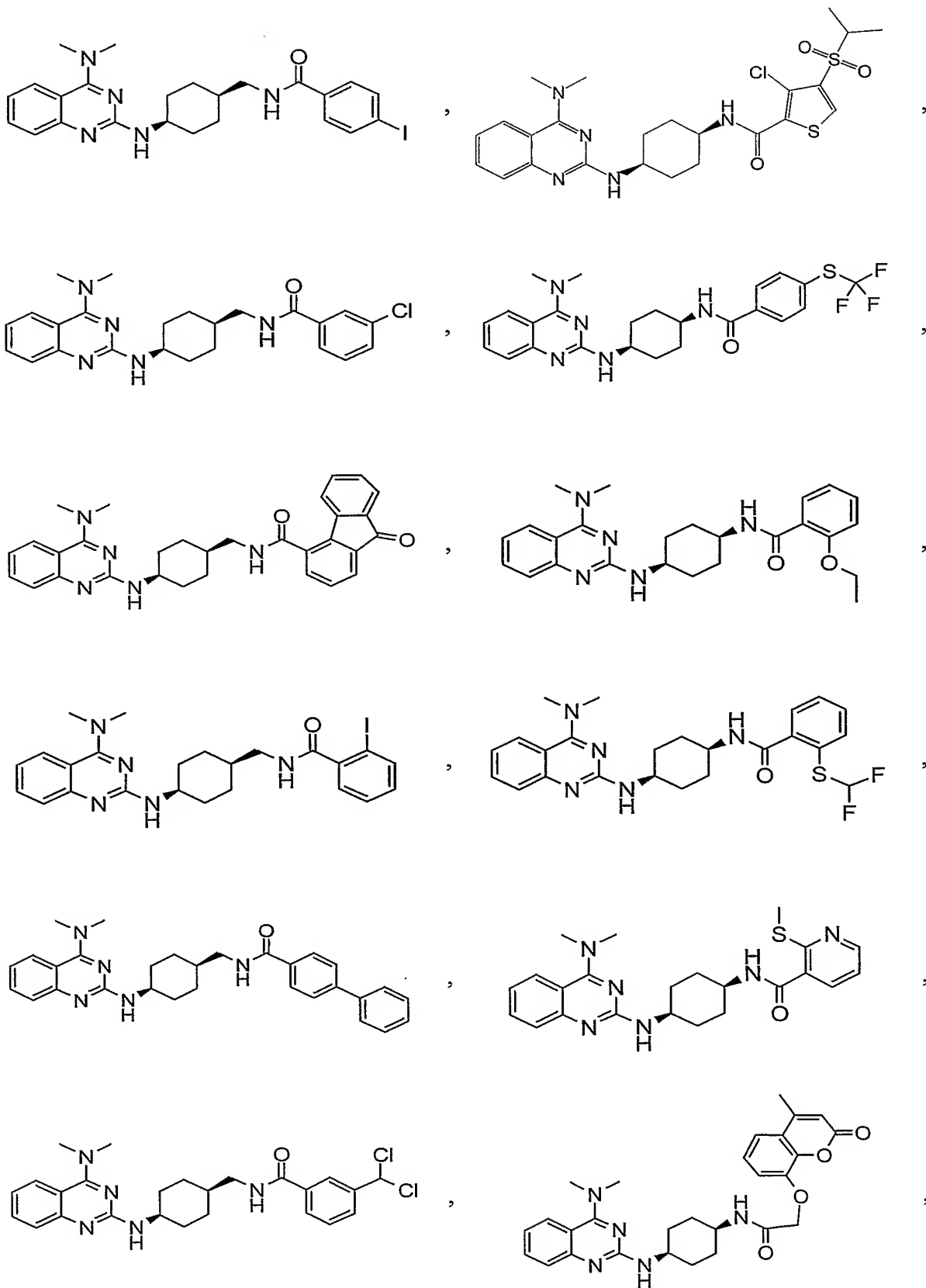
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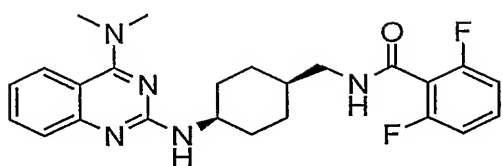


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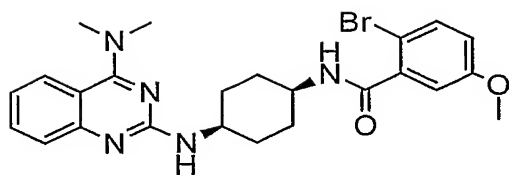




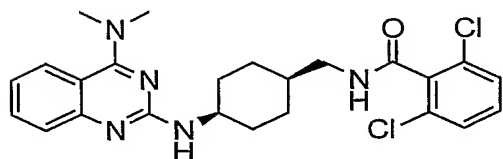




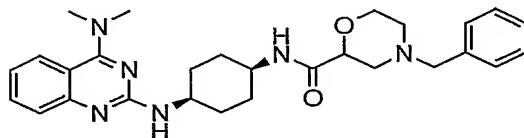
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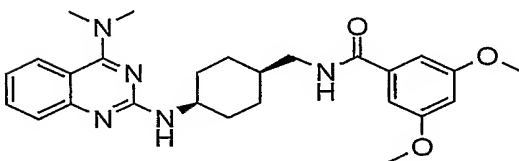
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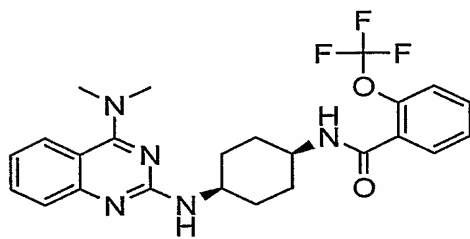
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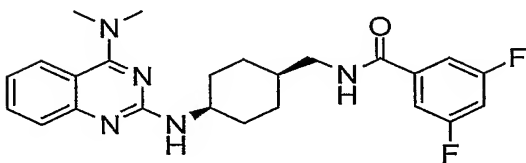
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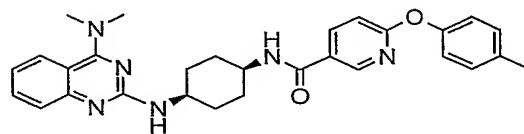
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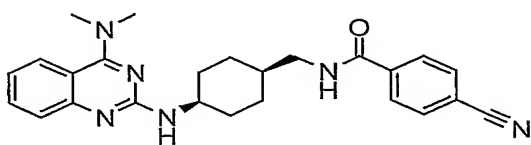
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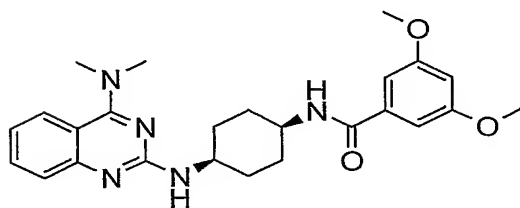
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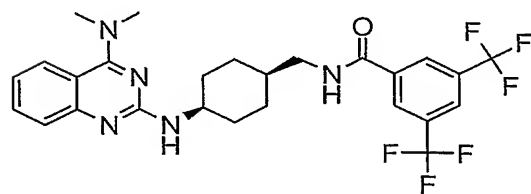
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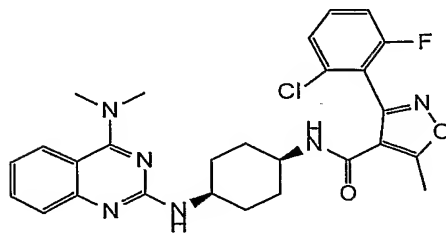
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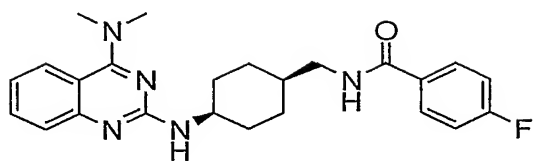
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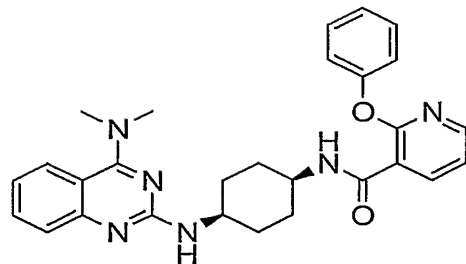
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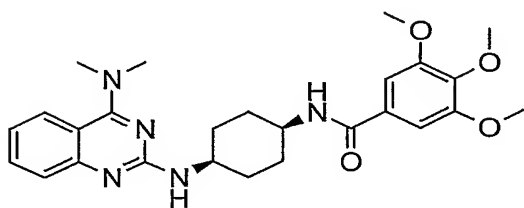
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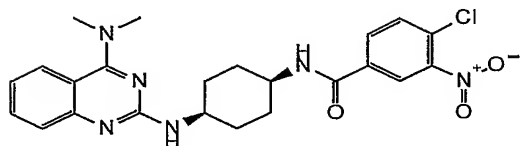
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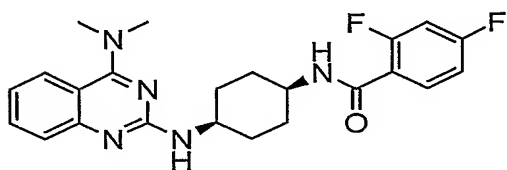
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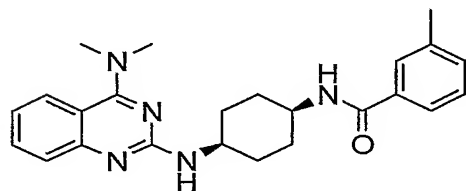
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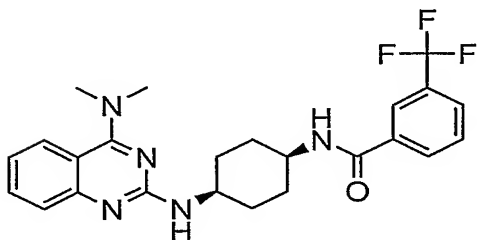
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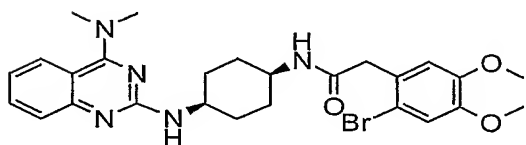
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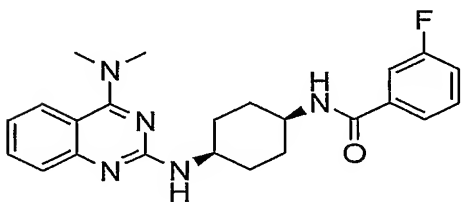
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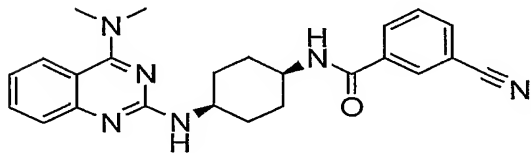
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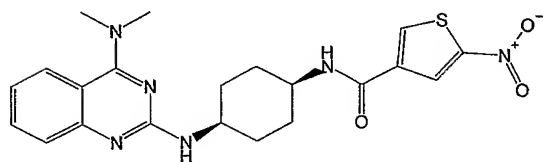
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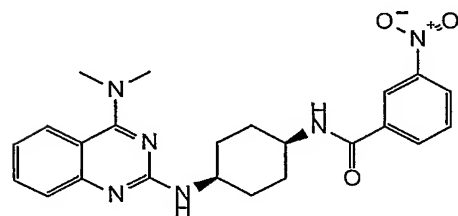
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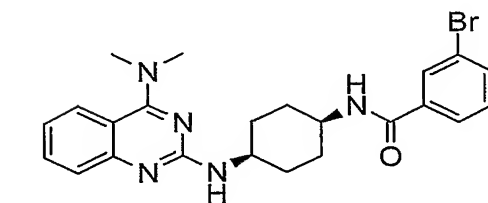
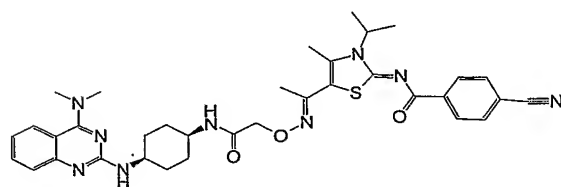
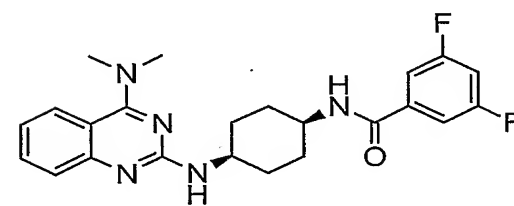
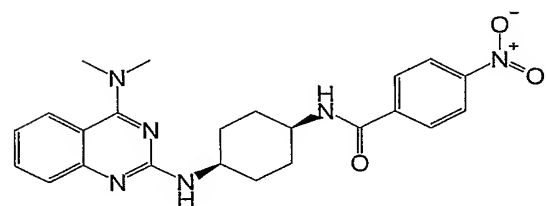
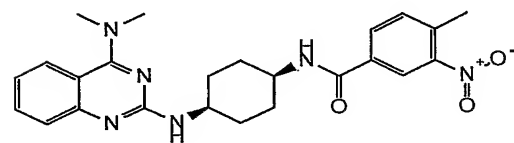
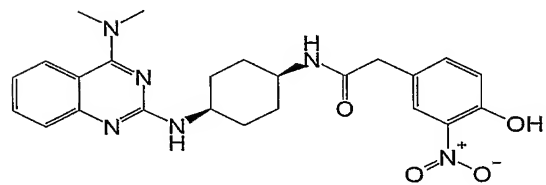
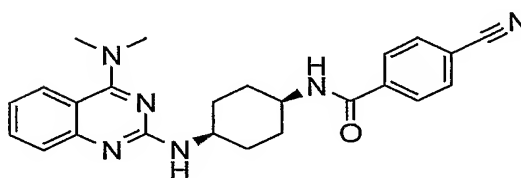
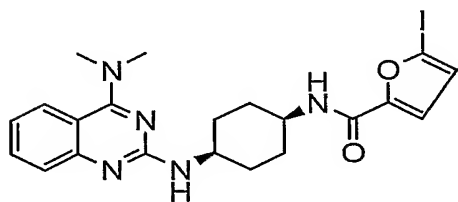
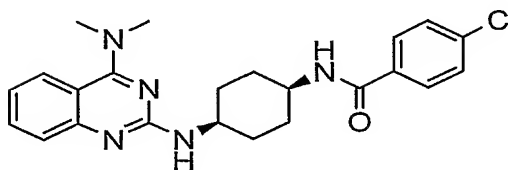
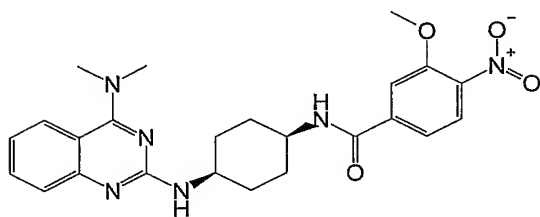
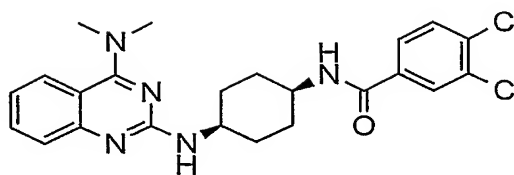
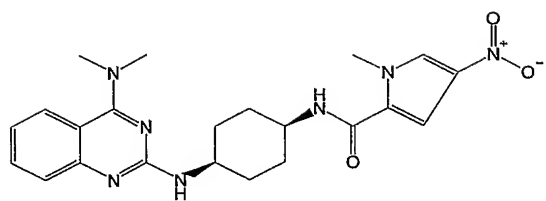
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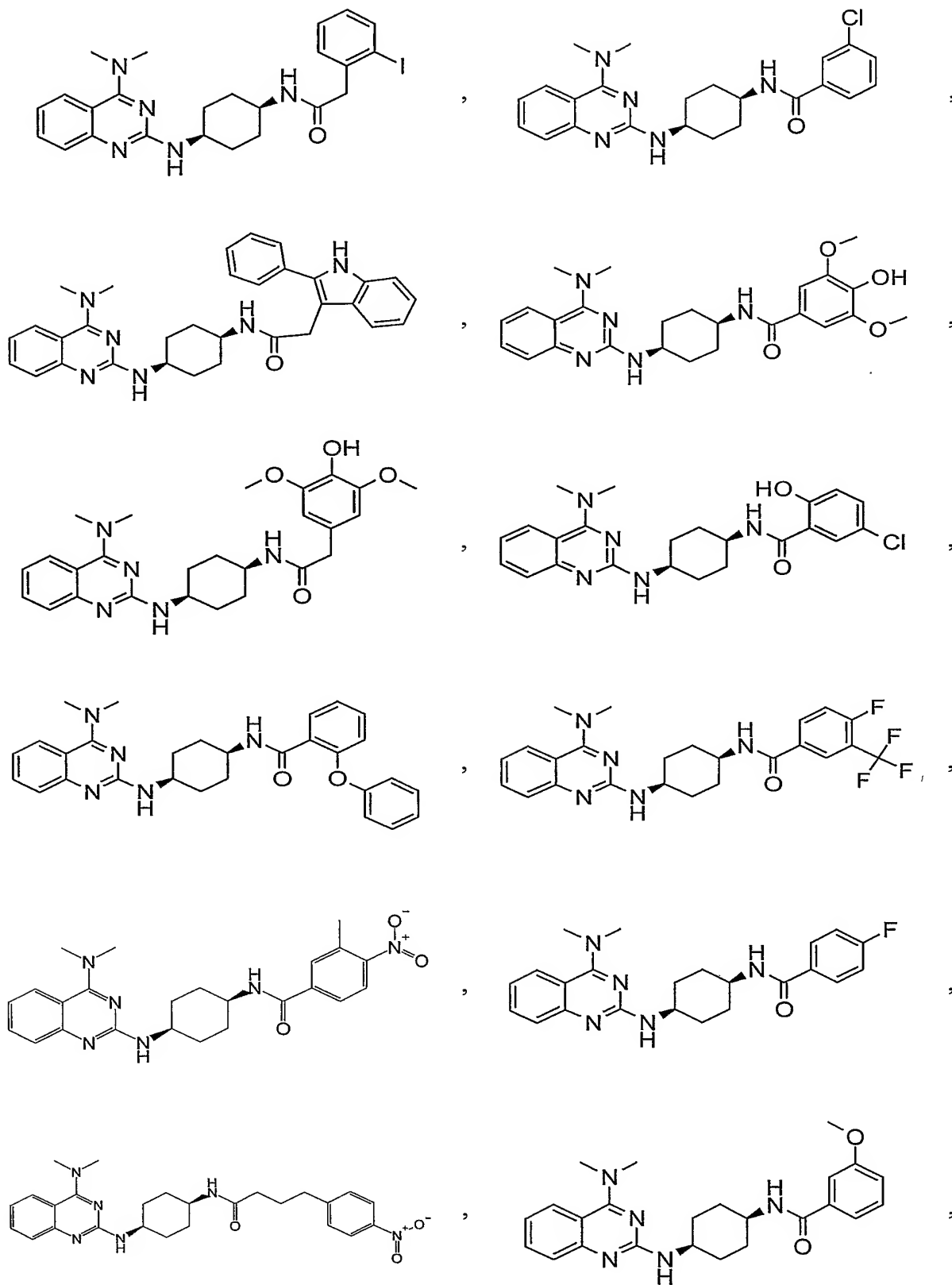


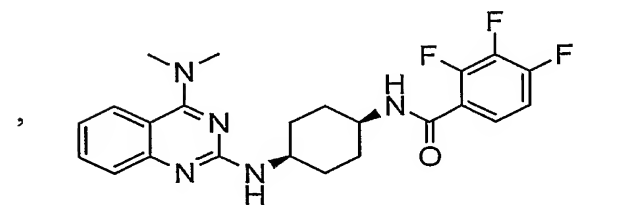
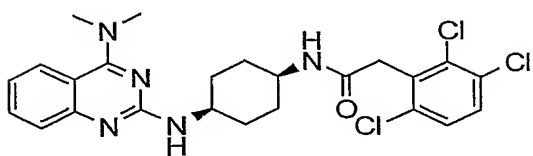
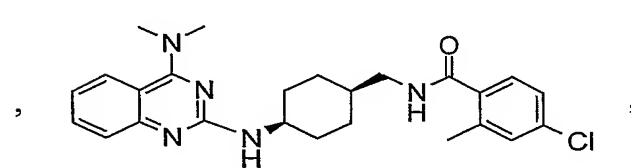
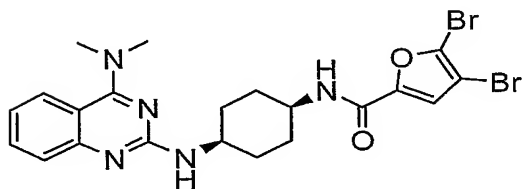
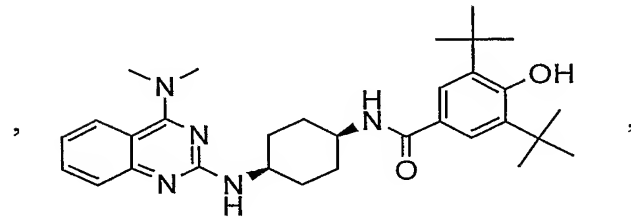
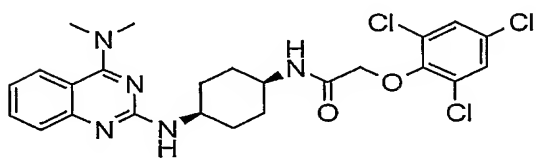
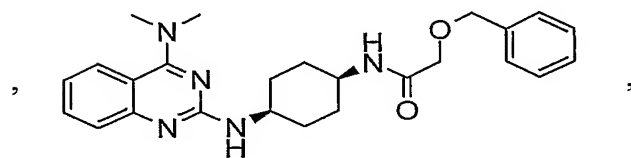
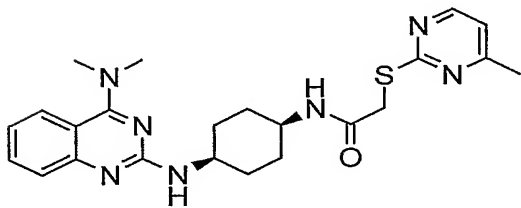
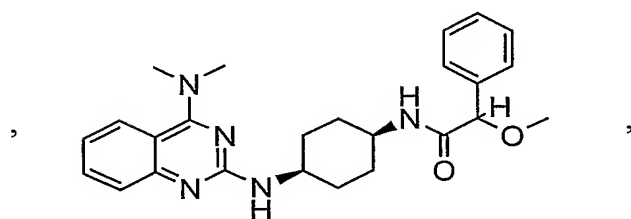
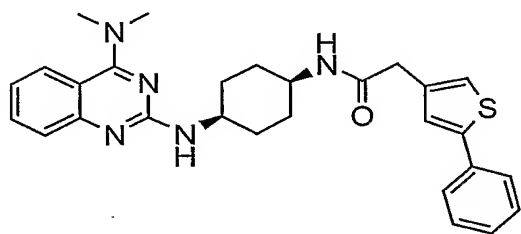
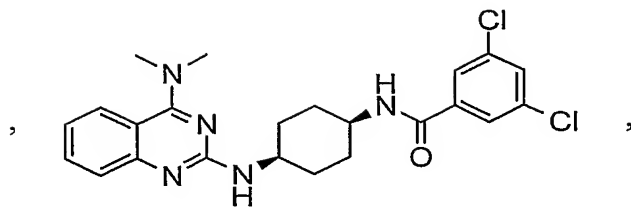
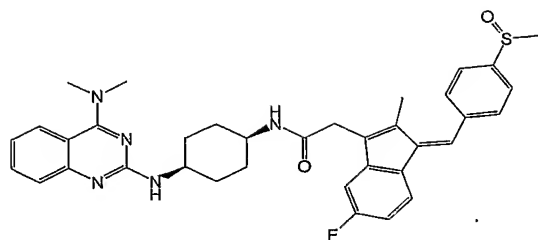
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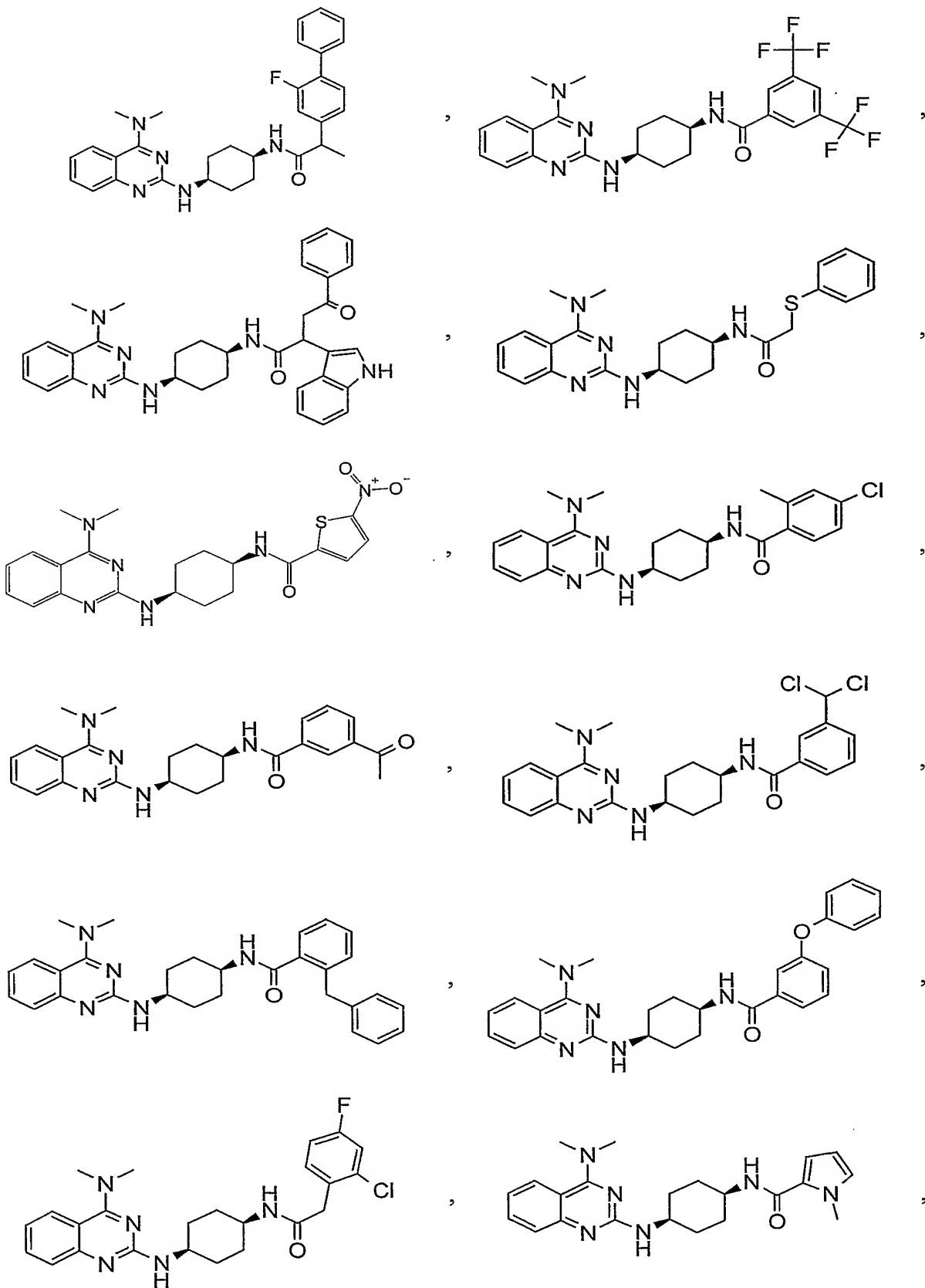


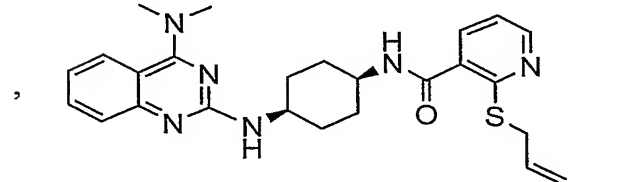
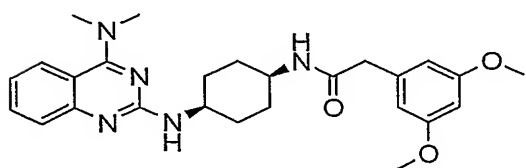
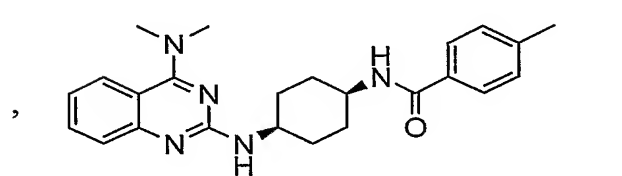
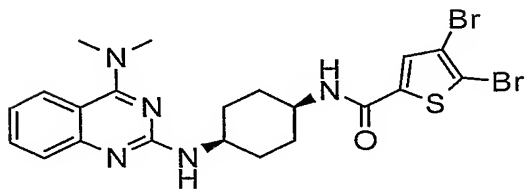
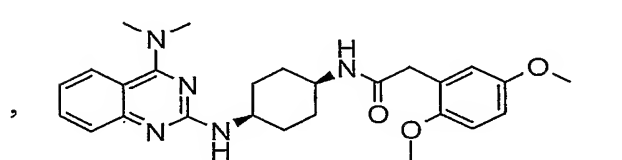
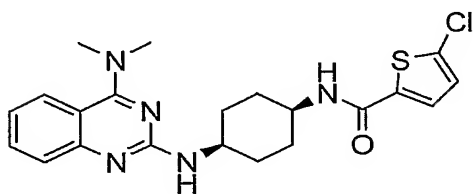
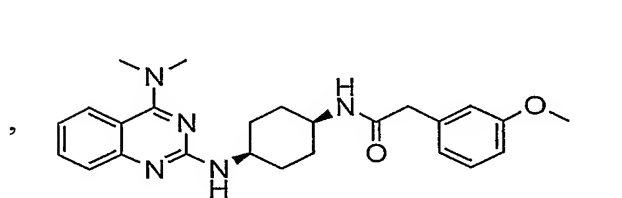
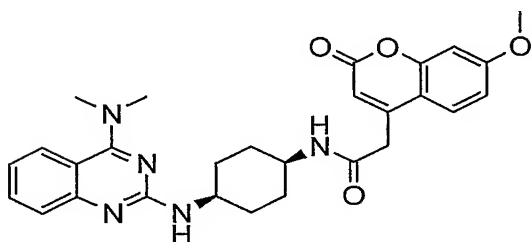
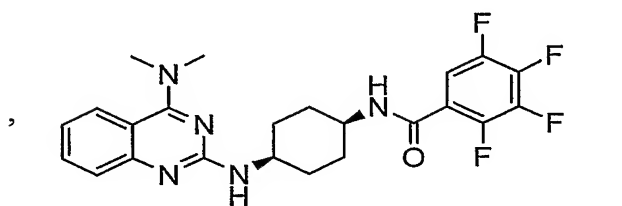
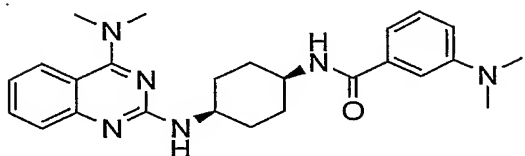
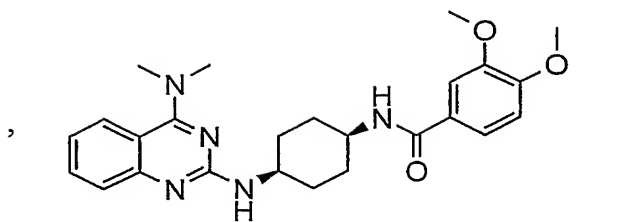
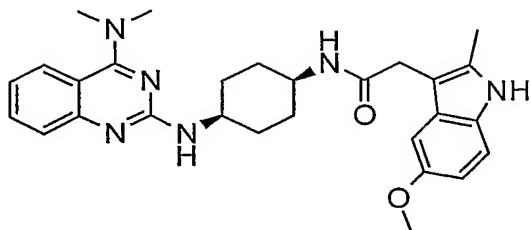
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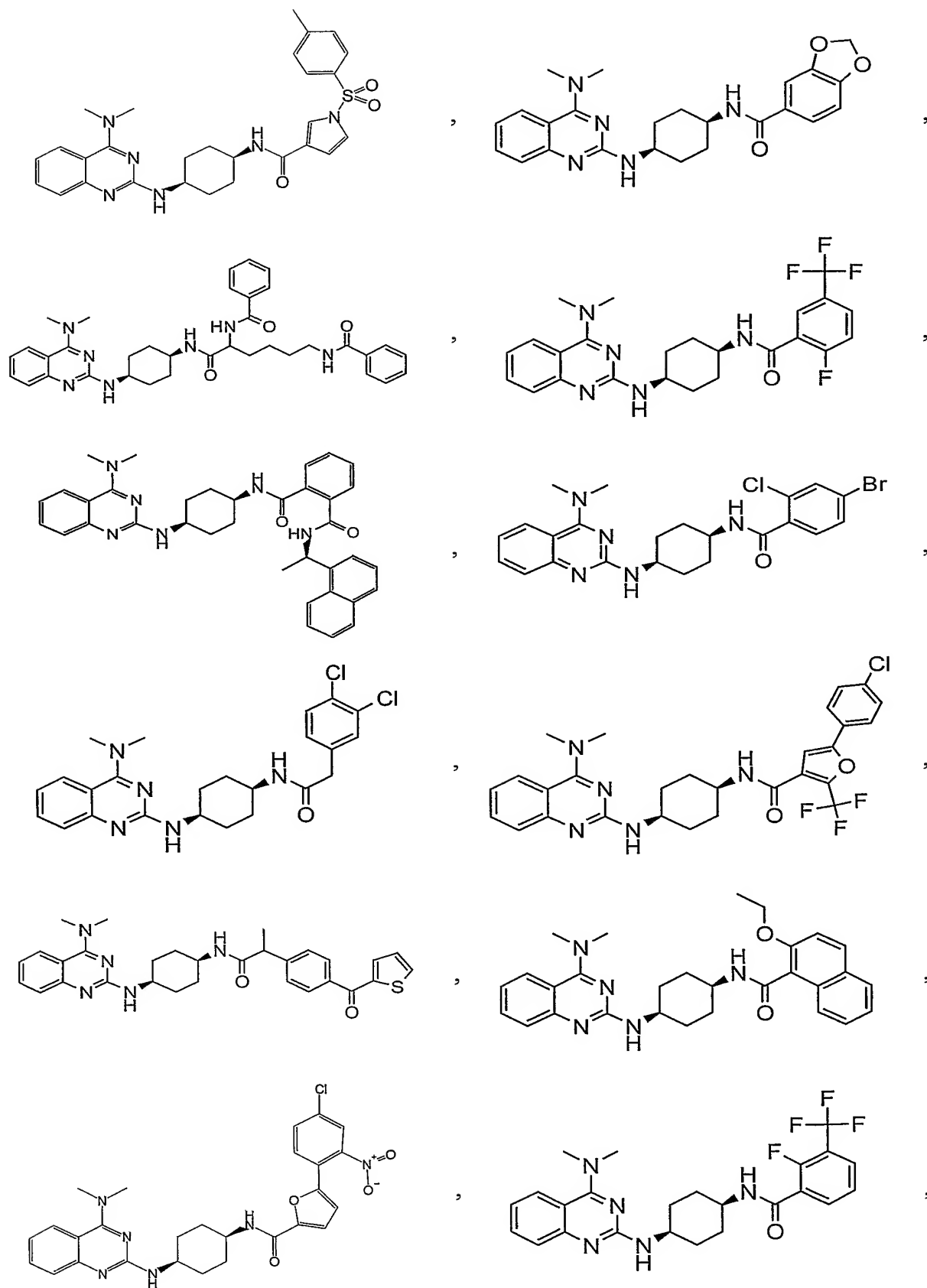


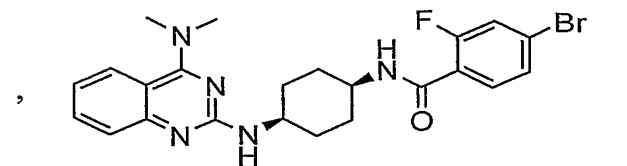
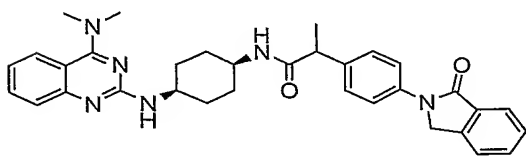
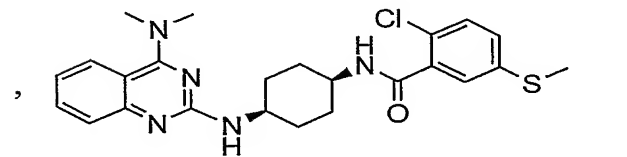
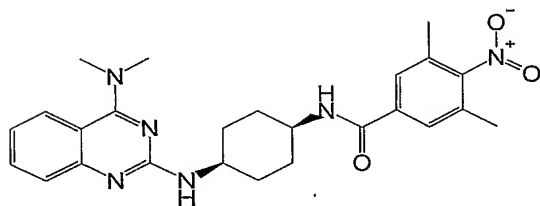
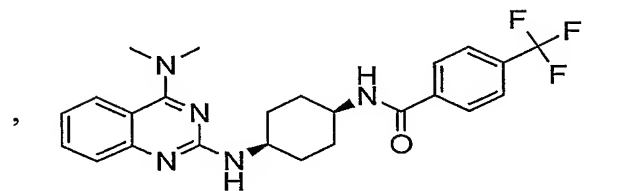
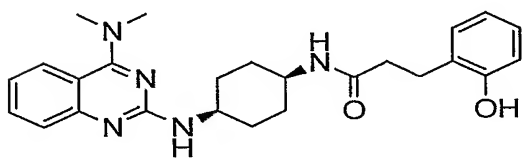
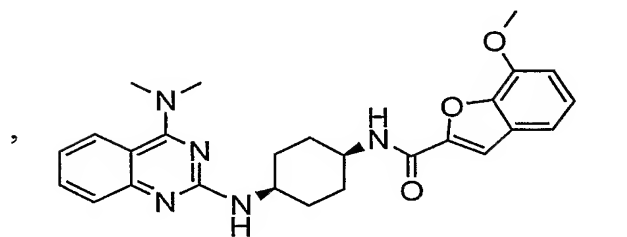
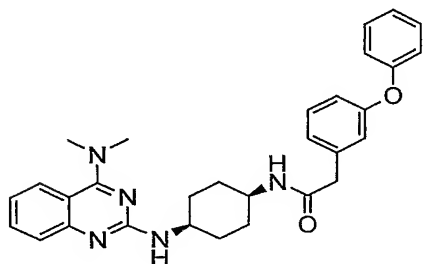
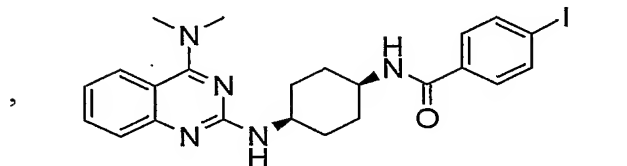
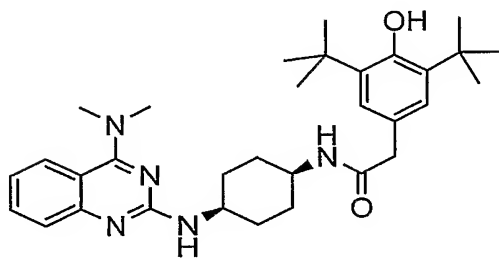
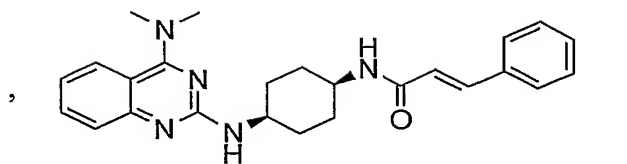
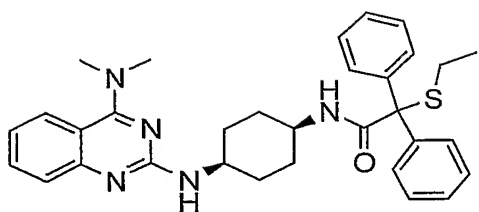


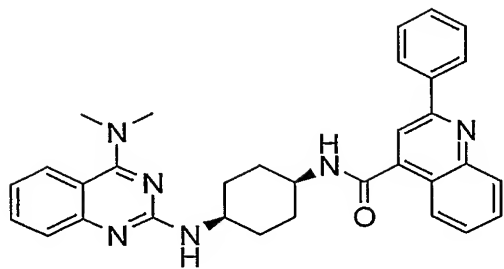




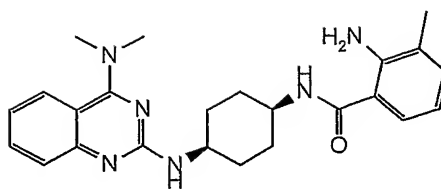




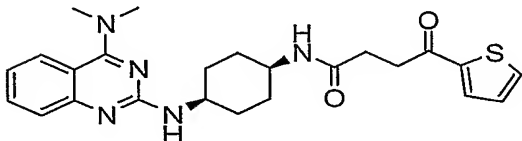




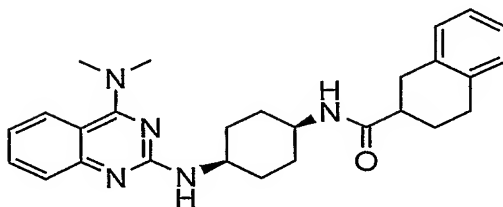
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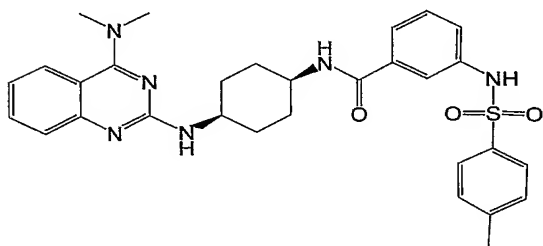
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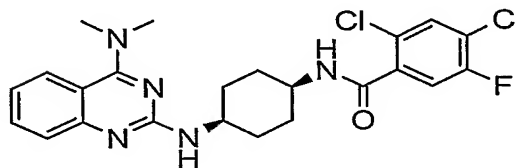
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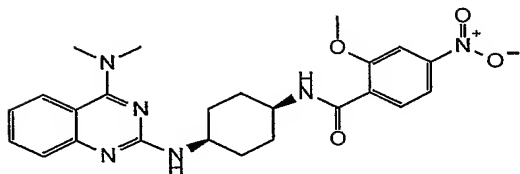
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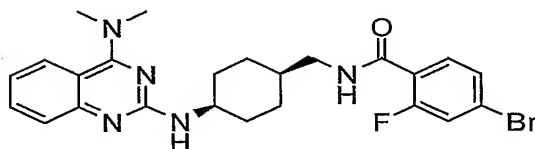
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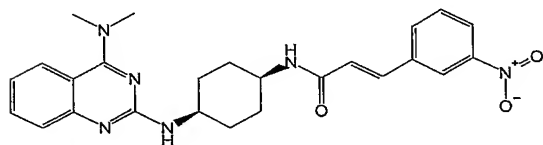
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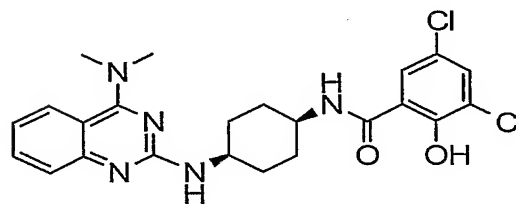
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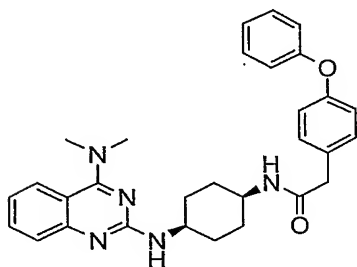
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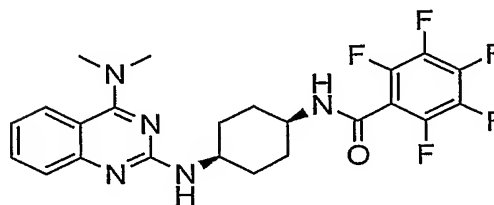
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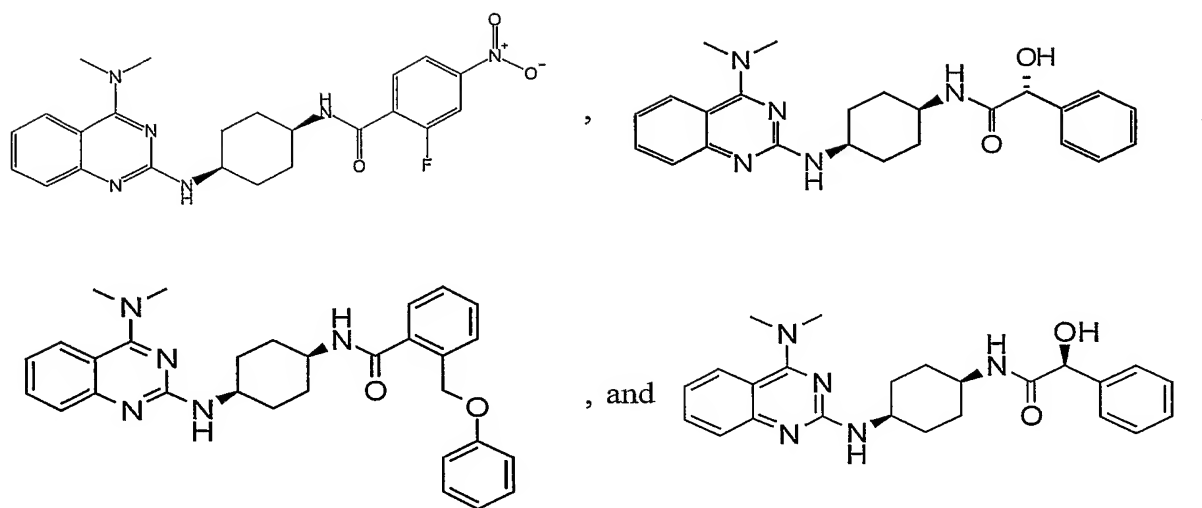
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; or, in case of, a salt thereof.

Other more preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₀ alkyl,

C₁-C₁₀ alkyl substituted by substituent(s) independently selected from

•C₅-C₆ cycloalkyl,

•carbocyclic aryl,

•heterocyclyl,

(ii) C₃-C₆ cycloalkyl,

(iii) carbocyclic aryl,

(iv) or heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula XX - XXII;

Y is -C(O)-;

wherein carbocyclic aryl is phenyl, naphthyl, anthranyl, or biphenyl;

heterocyclyl is 1,3-dioxo-isoindolyl, 1*H*-indolyl, 1-oxo-3*H*-isobenzofuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, 3,4-dihydro-2*H*-benzo[b][1,4]dioxepinyl, 4-oxo-3,4-dihydro-phthalazinyl, 9,10,10-trioxo-thioxanthenyl, 9*H*-xanthenyl, benzimidazolyl, benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[b]thienyl, furyl, imidazolyl, isoxazolyl, morpholino, oxolanyl, piperidyl, pyridyl, quinoxalyl, thienyl, quinolyl, or benzothiazolyl; halogen is fluoro, chloro, bromo, or iodo.

Further other more preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₄ alkyl,

C₁-C₄ alkyl substituted by substituent(s) independently selected from

•cyclopentyl,

•carbocyclic aryl,

•heterocyclyl,

(ii) carbocyclic aryl,

(iii) or heterocyclyl;

R_2 is methylamino or dimethylamino;

L is selected from Formula XX - XXII;

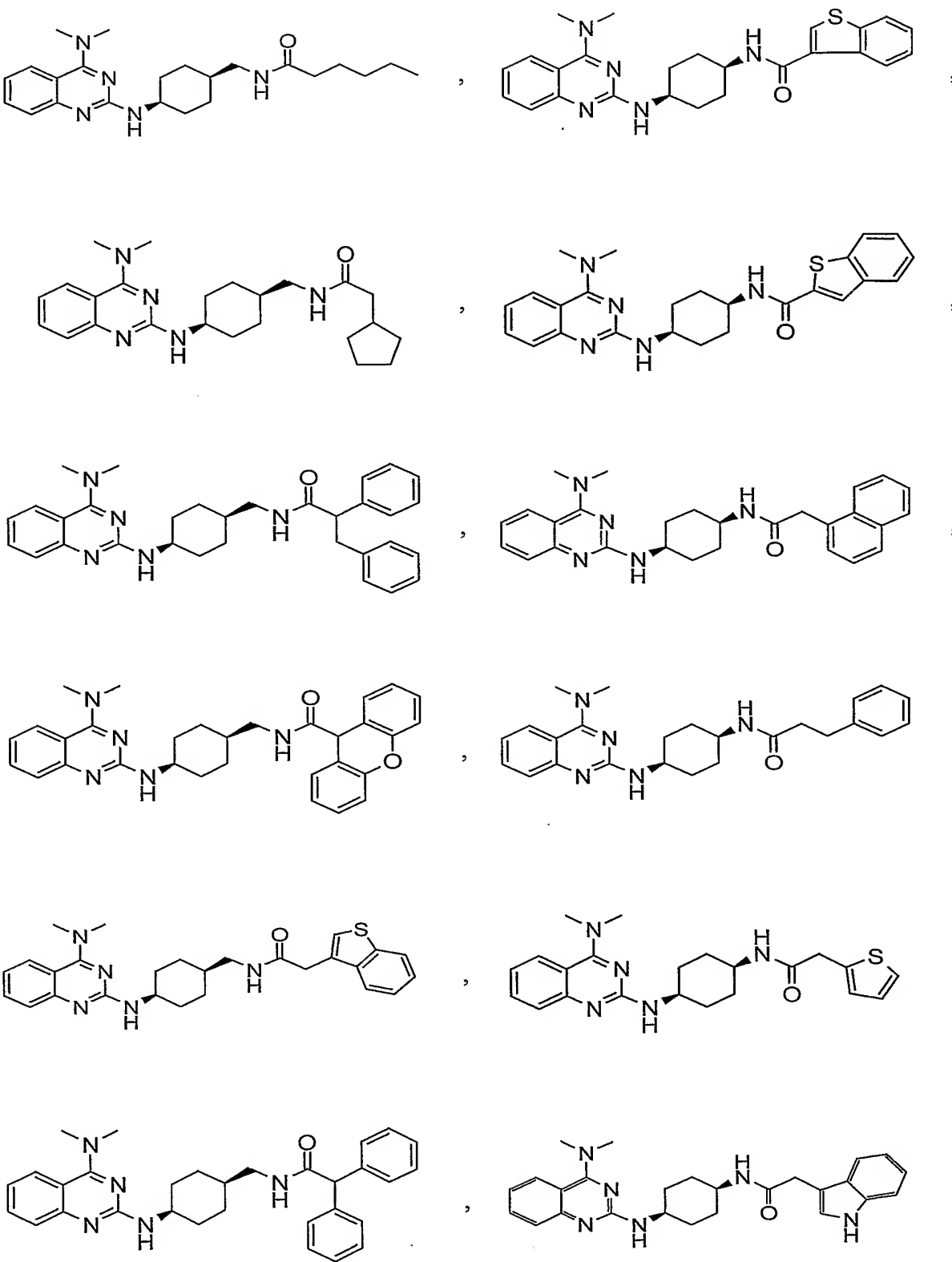
Y is -C(O)-;

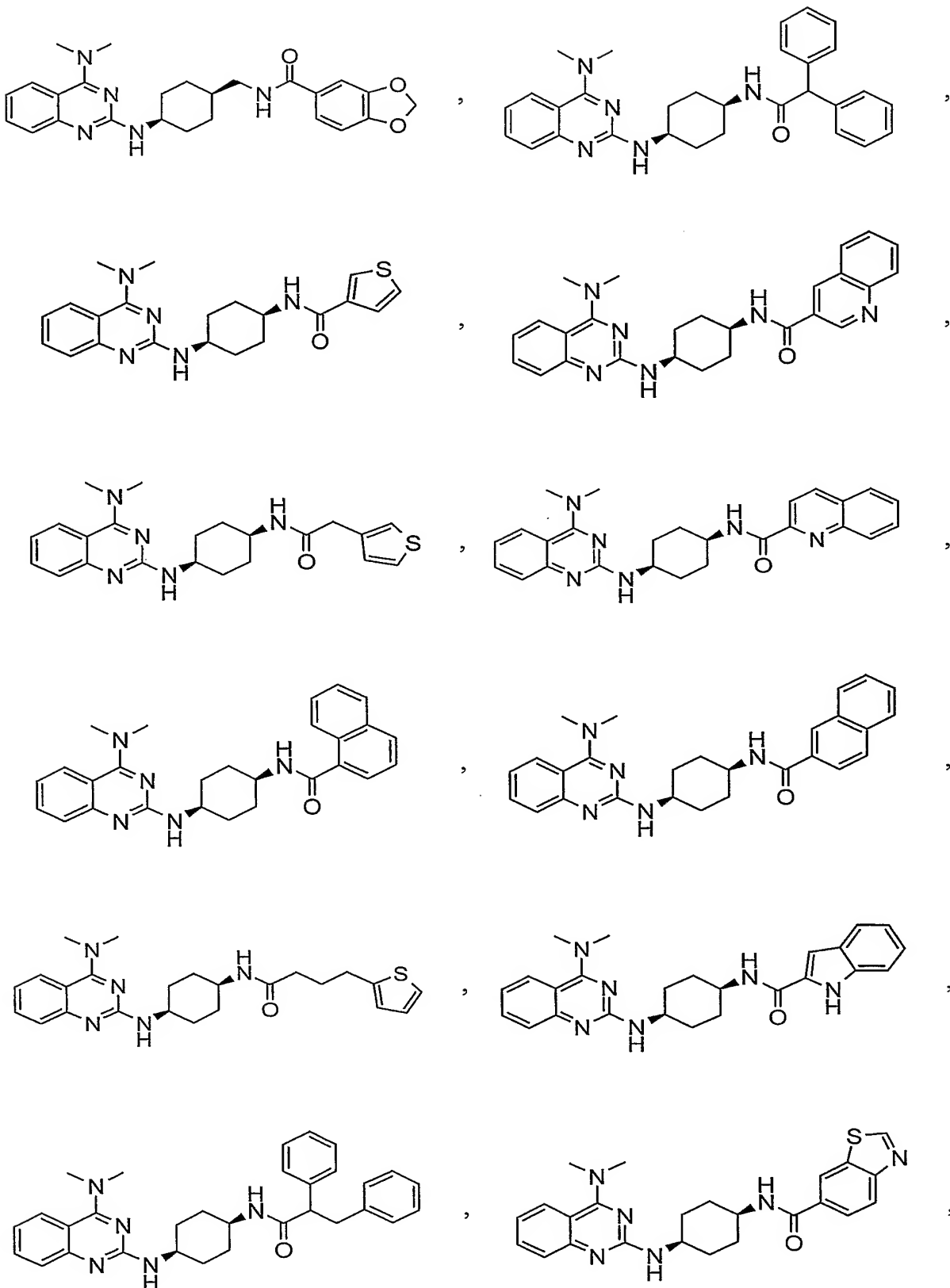
wherein carbocyclic aryl is phenyl, naphthyl, anthranyl, or biphenyl;

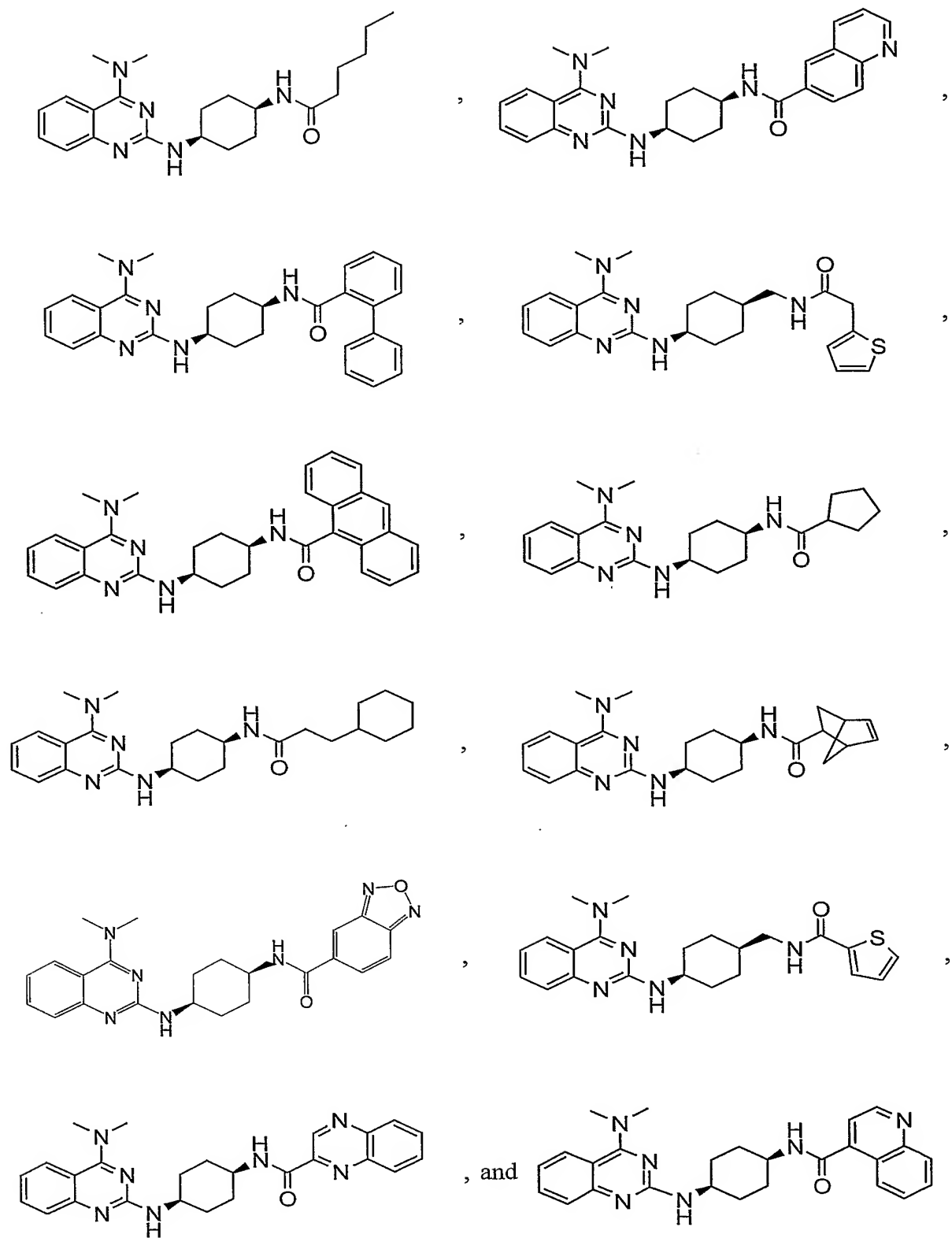
heterocyclyl is 9*H*-xanthenyl, benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[b]thienyl, thienyl, 1*H*-indolyl, quinoxalyl, quinolyl, or benzothiazolyl;

halogen is fluoro, chloro, bromo, or iodo.

The following compounds are specially preferred;







; or, in case of, a salt thereof.

Preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₀ alkyl,

C₁-C₁₀ alkyl substituted by substituent(s) independently selected from

- halogen,
- hydroxy,
- oxo,
- C₁-C₃ alkoxy,
- C₁-C₃ alkoxy substituted by substituent(s) independently selected from
 - carbocyclic aryl,
 - heterocyclyl,
 - heterocyclyl substituted by C₁-C₃ alkyl,
 - carbocyclic aryloxy,
 - carbocyclic aryloxy substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by C₁-C₃ alkoxy,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - mono- or di-C₁-C₃ alkylamino,
 - mono- or di-C₁-C₃ alkylamino substituted by carbocyclic aryl,
 - mono- or di-C₁-C₃ alkylamino substituted by halogenated carbocyclic aryl,
 - mono- or di-C₁-C₃ alkylamino,
 - mono- or di-C₁-C₃ alkylamino substituted by substituent(s) independently selected from
 - cyano,
 - carbocyclic aryl,
 - heterocyclyl,
 - mono- or di-carbocyclic arylamino,
 - mono- or di-carbocyclic arylamino substituted by C₁-C₃ alkyl,
 - C₁-C₃ alkylcarbonylamino,

- C₁-C₄ alkoxycarbonylamino,
- carbocyclic arylsulfonylamino,
- carbocyclic arylsulfonylamino substituted by substituent(s) independently selected from
 - nitro,
 - C₁-C₃ alkyl,
 - mono- or di-C₁-C₃ alkylamino,
- C₁-C₃ alkylthio,
- C₁-C₃ alkylthio substituted by substituent(s) independently selected from
 - mono- or di-carbocyclic arylamino,
 - halogenated mono- or di-carbocyclic arylamino,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkoxy,
- carbocyclic arylthio,
- carbocyclic arylthio substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
- carbocyclic arylsulfonyl,
- halogenated carbocyclic arylsulfonyl,
- heterocyclylthio,
- C₃-C₆ cycloalkyl,
- C₃-C₆ cycloalkyl substituted by C₁-C₃ alkyl,
- carbocyclyl,
- carbocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - C₂-C₃ alkenyl,
 - C₂-C₃ alkenyl substituted by carbocyclic aryl,
 - C₂-C₃ alkenyl substituted by carbocyclic aryl substituted C₁-C₃ alkylsulfinyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,
- hydroxy,
- nitro,
- C₁-C₄ alkyl,
- C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - carbocyclic aryl,
 - mono- or di-carbocyclic arylamino,
 - mono- or di-carbocyclic arylamino substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - halogenated C₁-C₃ alkoxy,
 - C₁-C₃ alkoxy,
 - C₁-C₃ alkoxy substituted by substituent(s) independently selected from
 - halogen,
 - carbocyclic aryl,
 - carbocyclic aryloxy,
 - C₁-C₃ alkoxycarbonyl,
 - mono- or di-C₁-C₃ alkylamino,
 - C₁-C₃ alkylthio,
 - halogenated C₁-C₃ alkylthio,
 - C₁-C₃ alkylsulfonyl,
 - C₃-C₆ cycloalkyl,
 - carbocyclic aryl,
 - heterocyclyl,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,

- C₁-C₃ alkoxy,
- C₁-C₃ alkoxy substituted by carbocyclic aryl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- (ii) C₂-C₈ alkenyl,
- C₂-C₈ alkenyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkoxy,
 - C₁-C₃ alkoxy substituted by carbocyclic aryl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - C₁-C₃ alkoxy,
 - halogenated C₁-C₃ alkoxy,
 - heterocyclyl,
 - heterocyclyl substituted by nitro,
- (iii) C₂-C₄ alkynyl,
- C₂-C₄ alkynyl substituted by carbocyclic aryl,
- (iv) C₃-C₆ cycloalkyl,
- C₃-C₆ cycloalkyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,
 - C₁-C₃ alkyl substituted by substituent(s) independently selected from
 - hydroxy,
 - oxo,
 - carbocyclic aryl,
 - mono- or di-C₁-C₃ alkylamino,
 - mono- or di-C₁-C₃ alkylamino substituted by carbocyclic aryl,
 - carbocyclic aryl,
- (v) C₃-C₆ cycloalkenyl,
- C₃-C₆ cycloalkenyl substituted by C₁-C₃ alkyl,
- (vi) carbocyclyl,

carbocyclyl substituted by substituent(s) independently selected from

- hydroxy,

- nitro,

(vii) carbocyclic aryl,

carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,

- hydroxy,

- cyano,

- nitro,

- C₁-C₉ alkyl,

- C₁-C₉ alkyl substituted by substituent(s) independently selected from

- halogen,

- hydroxy,

- oxo,

- C₁-C₃ alkoxy,

- carbocyclic aryloxy,

- mono- or di-C₁-C₃ alkylamino-N-oxy,

- mono- or di-C₁-C₃ alkylamino,

- mono- or di-C₁-C₃ alkylamino substituted by carbocyclic aryl,

- mono- or di-carbocyclic arylamino,

- mono- or di-carbocyclic arylamino substituted by C₁-C₃ alkoxy,

- carbocyclic aryl,

- halogenated carbocyclic aryl,

- heterocyclyl,

- heterocyclyl substituted by C₁-C₃ alkyl,

- C₂-C₃ alkenyl,

- C₂-C₃ alkenyl substituted by carbocyclic aryl,

- C₁-C₉ alkoxy,

- C₁-C₉ alkoxy substituted by substituent(s) independently selected from

- hydroxy,

- halogen,

- carboxy,

- mono- or di-C₁-C₃ alkylamino,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- C₂-C₃ alkenyloxy,
- C₁-C₃ alkylcarbonyloxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by substituent(s) independently selected from
- halogen,
- C₁-C₄ alkyl,
- halogenated C₁-C₄ alkyl,
- C₁-C₃ alkoxy,
- heterocyclyloxy,
- heterocyclyloxy substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- (carbocyclic aryl)S(O)₂O,
- carboxy,
- C₁-C₃ alkoxycarbonyl,
- mono- or di-C₁-C₃ alkylaminocarbonyl,
- mono- or di-C₁-C₃ alkylaminocarbonyl substituted by carbocyclic aryl,
- amino,
- mono- or di-C₁-C₄ alkylamino,
- mono- or di-C₁-C₄ alkylamino substituted by cyano,
- mono- or di-carbocyclic arylamino,

- C₁-C₃ alkylcarbonylamino,
- carbocyclic arylsulfonylamino,
- carbocyclic arylsulfonylamino substituted by C₁-C₃ alkyl,
- (carbocyclic aryl)NHC(O)NH,
- (carbocyclic aryl)NHC(O)NH substituted by C₁-C₃ alkoxy,
- (carbocyclic aryl)NHC(O)NH substituted by halogenated C₁-C₃ alkoxy,
- C₁-C₃ alkylthio,
- halogenated C₁-C₃ alkylthio,
- carbocyclic arylthio,
- halogenated carbocyclic arylthio,
- carbocyclic arylthio substituted by C₁-C₃ alkyl,
- heterocyclylthio,
- C₁-C₃ alkylsulfonyl,
- mono- or di-C₁-C₃ alkylaminosulfonyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - C₁-C₇ alkyl,
 - halogenated C₁-C₇ alkyl,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
- (viii) heterocyclyl,
- or heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,

- hydroxy,
- oxo,
- C₁-C₃ alkylcarbonyloxy,
- C₁-C₃ alkoxycarbonyl,
- C₁-C₃ alkylthio,
- C₁-C₃ alkylthio substituted by carbocyclic aryl,
- C₁-C₃ alkylthio substituted by halogenated carbocyclic aryl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
- heterocyclyl,
- C₁-C₃ alkoxy,
- C₁-C₃ alkoxy substituted by carbocyclic aryl,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by C₁-C₃ alkyl,
- mono- or di-C₁-C₃ alkylamino,
- C₁-C₄ alkylcarbonylamino,
- C₁-C₃ alkylthio,
- carbocyclic arylthio,
- halogenated carbocyclic arylthio,
- carbocyclic arylthio substituted by C₁-C₃ alkoxycarbonyl,
- heterocyclylthio,
- heterocyclylthio substituted by C₁-C₃ alkyl,
- C₁-C₃ alkylsulfonyl,
- carbocyclic arylsulfonyl,
- carbocyclic arylsulfonyl substituted by C₁-C₄ alkyl,
- C₁-C₃ alkoxycarbonyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,

- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- halogenated C₁-C₃ alkoxy,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- C₁-C₃ alkoxycarbonyl;

R₂ is -NHNH₂, -NHNHBoc, -N(R_{2a})(R_{2b}), morpholino, 4-acetyl-piperazyl, or 4-phenyl-piperazyl;

wherein R_{2a} is H or C₁-C₃ alkyl;

R_{2b} is C₁-C₄ alkyl, C₁-C₄ alkyl substituted by substituent(s) independently selected from

- hydroxy,
 - C₁-C₃ alkoxy,
 - amino,
 - NHBoc,
 - C₃-C₆ cycloalkyl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - SO₂NH₂,
 - heterocyclyl,
 - C₃-C₆ cycloalkyl, carbocyclic aryl, carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
- or a group of Formula IV;

wherein Boc is carbamic acid *tert*-butyl ester and R₃ is C₁-C₃ alkyl or C₁-C₃ alkyl substituted by substituent(s) independently selected from

- carbocyclic aryl,
- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by C₁-C₃ alkoxy;

L is selected from Formula V - XIX;

wherein R₄ is H or C₁-C₃ alkyl;

R₅ is H, C₁-C₃ alkyl, or C₁-C₃ alkyl substituted by a substituted carbocyclic aryl;

Y is -(CH₂)_m, m is 0 or 1;

wherein carbocyclic aryl is phenyl, naphthyl, phenanthryl, or biphenyl;

carbocyclyl is 9*H*-fluorenyl, 9-oxo-fluorenyl, acenaphthyl, anthraquinonyl, indanyl, or indenyl;

heterocyclyl is 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,2-dihydro-3-oxo-pyrazolyl, 1,3,4-thiadiazolyl, 1,3-dioxo-isoindolyl, 1,3-dioxolanyl, 1*H*-indolyl, 1*H*-pyrrolo[2,3-*c*]pyridyl, 1*H*-pyrrolyl, 2,2',5',2''-terthiophenyl, 2,2'-bithiophenyl, 2,3-dihydro-1-oxo-isoindolyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2,3-dihydro-benzofuryl, 2,4-dihydro-3-oxo-pyrazolyl, 2*H*-benzopyranyl, 2-oxo-pyrrolidinyl, 3,4-dihydro-2*H*-benzo[1,4]oxazinyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepinyl, 4*H*-benzo[1,3]dioxinyl, 4*H*-benzopyranyl, 4-oxo-1,5,6,7-tetrahydro-indolyl, 4-oxo-benzopyranyl, 9*H*-carbazolyl, 9*H*-xanthenyl, azetidiny, benzimidazolyl, benzo[1,3]dioxolyl, benzo[*b*]thienyl, benzofuryl, benzothiazolyl, furyl, imidazo[2,1-*b*]thiazolyl, imidazolyl, isoxazolyl, morpholino, morpholinyl, oxolanyl, piperazyl, piperidyl, pyrazolo[5,1-*b*]thiazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolidyl, quinolyl, quinoxalyl, thiazolidyl, thiazolyl, thienyl, or thiolanyl;

halogen is fluoro, chloro, bromo, or iodo.

Other preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₀ alkyl substituted by substituent(s) independently selected from

- methoxy,
- methoxy substituted by carbocyclic aryl,

- carbocyclic aryloxy,
- halogenated carbocyclic aryloxy,
- mono-C₁-C₂ alkylamino substituted by cyano,
- mono- or di-C₁-C₂ alkylamino substituted by carbocyclic aryl,
- mono-carbocyclic arylamino,
- mono-carbocyclic arylamino substituted by methyl,
- carbocyclic arylsulfonylamino substituted by methyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by carbocyclic aryl,
 - C₁-C₄ alkyl substituted by hydroxy,
 - C₁-C₂ alkoxy,
 - halogenated C₁-C₂ alkoxy,
 - heterocyclyl substituted by carbocyclic aryl,
- (ii) C₂-C₈ alkenyl substituted by substituent(s) independently selected from
 - methoxy substituted by carbocyclic aryl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by methoxy,
- (iii) C₂-C₄ alkynyl substituted by carbocyclic aryl,
- (iv) cyclohexyl substituted by carbocyclic arylmethyl,
- (v) carbocyclyl,
- (vi) carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - amino,
 - C₁-C₉ alkyl,
 - halogenated C₁-C₉ alkyl,

- C₁-C₉ alkoxy,
- C₁-C₉ alkoxy substituted by substituent(s) independently selected from
 - halogen,
 - halogenated carbocyclic aryl,
- propenyloxy,
- methylamino,
- di-C₁-C₂ alkylamino,
- di-C₁-C₂ alkylamino substituted by cyano,
- methylthio,
- halogenated methylthio,
- (vii) heterocyclyl,
- or heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by hydroxy,
 - C₁-C₄ alkyl substituted by carbocyclic aryl,
 - methoxy,
 - C₁-C₂ alkoxy carbonyl,
 - carbocyclic arylthio substituted by methoxycarbonyl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - halogenated methyl,
- heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula Va, VIIIa, or IXa;

wherein R₄ and R₅ are independently selected from H or C₁-C₃ alkyl;

Y is -(CH₂)_m, m is 0 or 1;

wherein carbocyclic aryl is phenyl, naphthyl, phenanthryl, or biphenyl;

carbocyclyl is 9H-fluorenyl, acenaphthyl, or anthraquinonyl;

heterocyclyl is 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,2-dihydro-3-oxo-pyrazolyl, 1,3-dioxolanyl, 1H-indolyl, 1H-pyrrolyl, 2,2',5',2"-terthiophenyl, 2,2'-bithiophenyl, 2,3-

dihydro-benzo[1,4]dioxinyl, 3,4-dihydro-2*H*-benzo[1,4]oxazinyl, 4-oxo-benzopyranyl, 9*H*-carbazolyl, 9*H*-xanthenyl, benzimidazolyl, benzo[1,3]dioxolyl, benzo[*b*]thienyl, benzofuryl, benzothiazolyl, furyl, imidazolyl, isoxazolyl, oxolanyl, pyrazolo[5,1-*b*]thiazolyl, pyrazolyl, pyridyl, pyrimidyl, quinolyl, quinoxalyl, thiazolidyl, thiazolyl, thienyl, 2*H*-benzopyranyl, 4*H*-benzo[1,3]dioxinyl, azetidiny, imidazo[2,1-*b*]thiazolyl, morpholinyl, or 2,3-dihydro-benzofuryl;

halogen is fluoro, chloro, bromo, or iodo.

Other more preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₇ alkyl substituted by substituent(s) independently selected from

- methoxy,
- methoxy substituted by carbocyclic aryl,
- carbocyclic aryloxy,
- halogenated carbocyclic aryloxy,
- mono-ethylamino substituted by cyano,
- di-methylamino substituted by carbocyclic aryl,
- mono-carbocyclic arylamino,
- mono-carbocyclic arylamino substituted by methyl,
- carbocyclic arylsulfonylamino substituted by methyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by carbocyclic aryl,
 - C₁-C₄ alkyl substituted by hydroxy,
 - methoxy,
 - halogenated methoxy,
 - heterocyclyl substituted by carbocyclic aryl,

(ii) C₂-C₇ alkenyl substituted by substituent(s) independently selected from

- methoxy substituted by carbocyclic aryl,
- carbocyclic aryl,
- carbocyclic aryl substituted by methoxy,

(iii) butynyl substituted by carbocyclic aryl,

(iv) cyclohexyl substituted by carbocyclic arylmethyl,

(v) carbocyclyl,

(vi) carbocyclic aryl,

carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,
- hydroxy,
- cyano,
- amino,
- C₁-C₂ alkyl,
- halogenated methyl,
- C₁-C₃ alkoxy,
- C₁-C₃ alkoxy substituted by substituent(s) independently selected from
- halogen,
- halogenated carbocyclic aryl,
- propenyloxy,
- di-C₁-C₂ alkylamino,
- di-C₁-C₂ alkylamino substituted by cyano,
- methylthio,
- halogenated methylthio,

(vii) heterocyclyl,

or heterocyclyl substituted by substituent(s) independently selected from

- halogen,
- C₁-C₃ alkyl,
- C₁-C₃ alkyl substituted by hydroxy,
- C₁-C₃ alkyl substituted by carbocyclic aryl,
- methoxy,
- ethoxycarbonyl,

- carbocyclic arylthio substituted by methoxycarbonyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - halogenated methyl,
- heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula XX - XXII;

Y is -(CH₂)_m, m is 0 or 1;

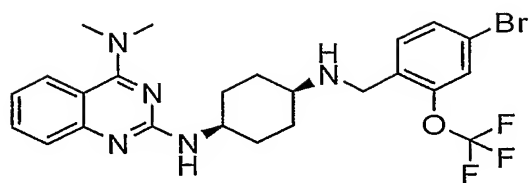
wherein carbocyclic aryl is phenyl, **naphthyl**, or biphenyl;

carbocyclyl is acenaphthyl;

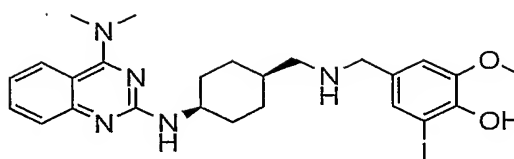
heterocyclyl is 1*H*-indolyl, 1*H*-pyrrolyl, 2,3-dihydro-benzo[1,4]dioxinyl, 9*H*-carbazolyl, benzo[1,3]dioxolyl, furyl, pyrazolyl, thienyl, 4-oxo-benzopyranyl, azetidiny, imidazo[2,1-*b*]thiazolyl, pyridyl, imidazolyl, 2,3-dihydro-benzofuryl, or benzo[*b*]thienyl;;

halogen is fluoro, chloro, bromo, or iodo.

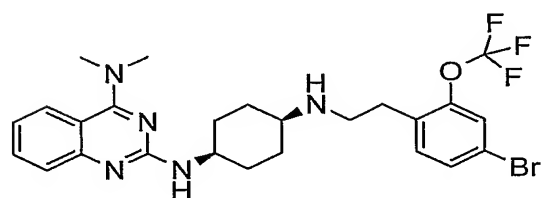
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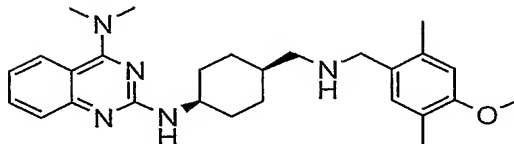
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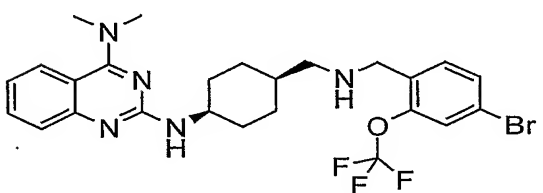
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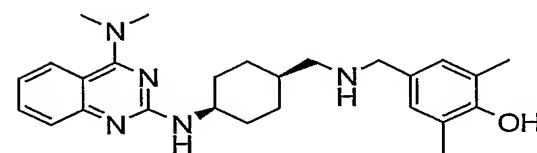
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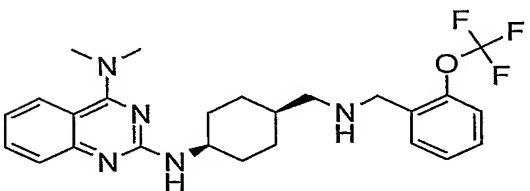
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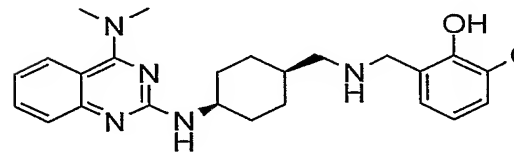
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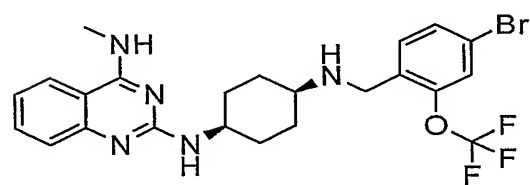
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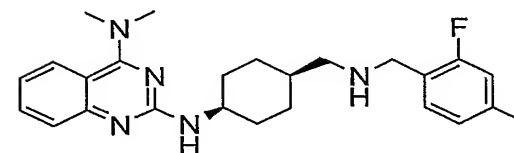
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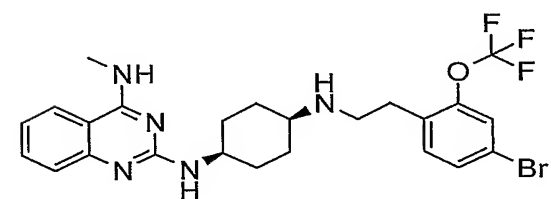
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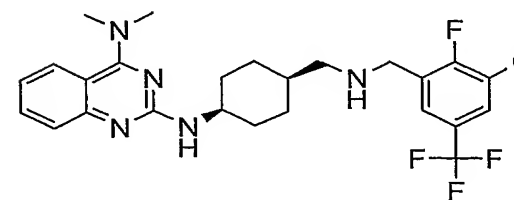
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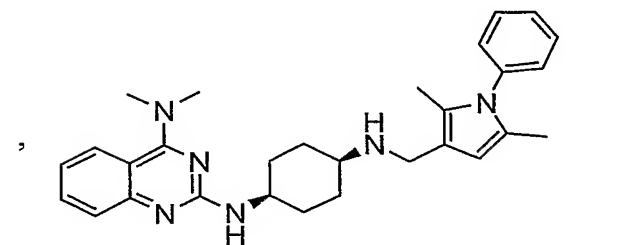
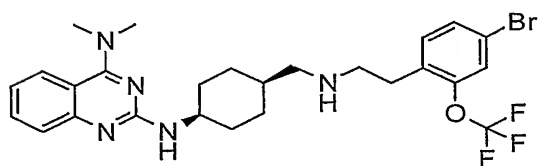
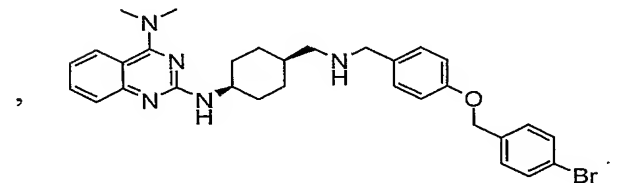
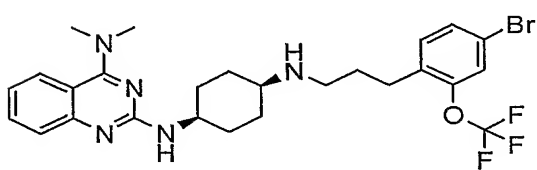
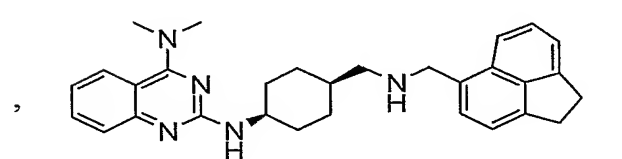
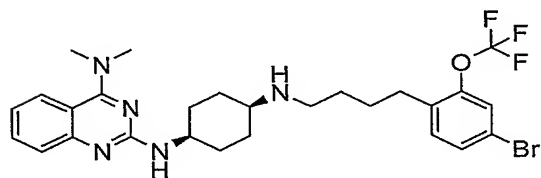
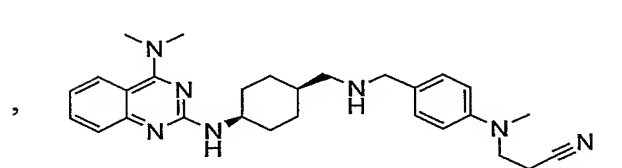
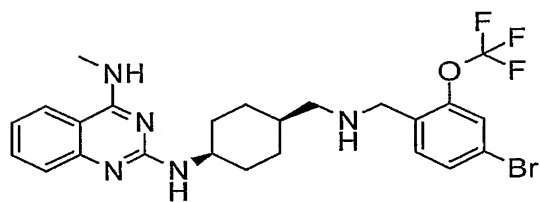
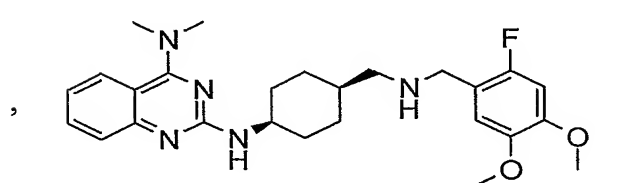
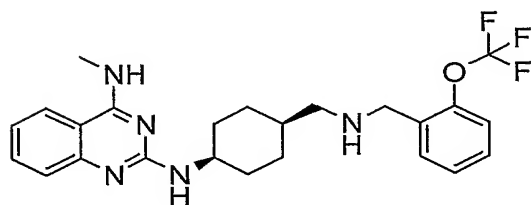
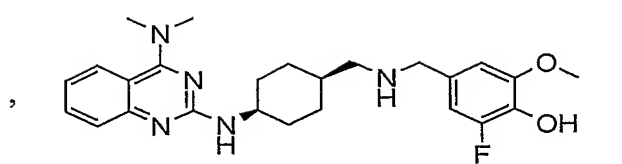
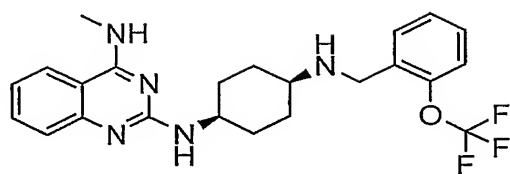
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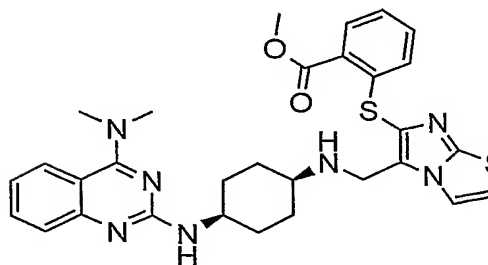
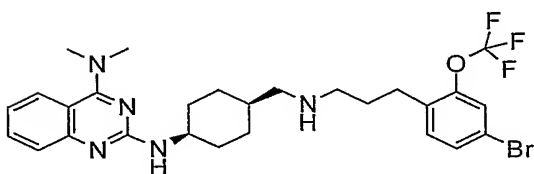
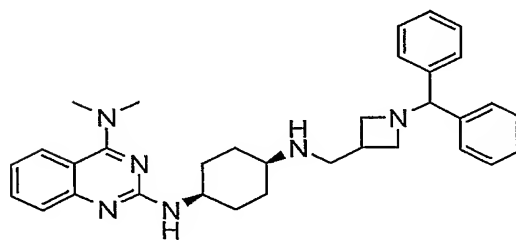
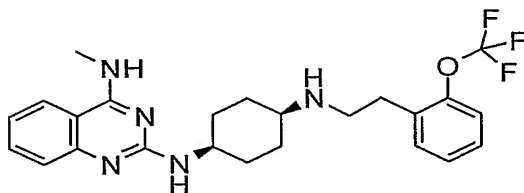
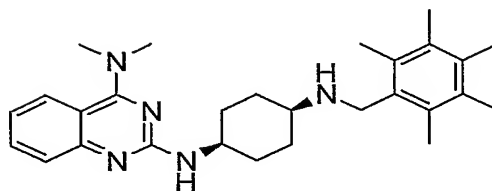
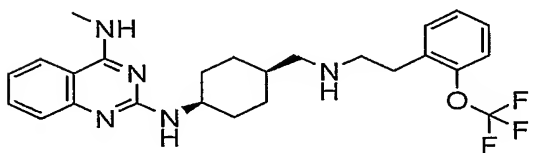
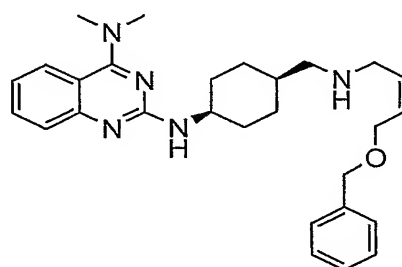
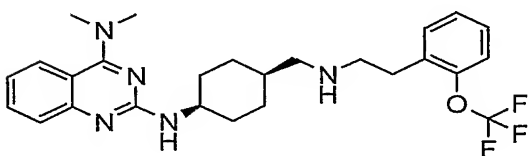
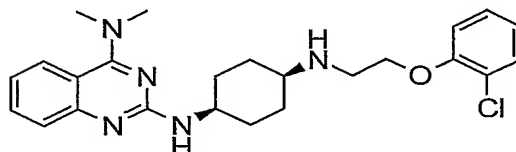
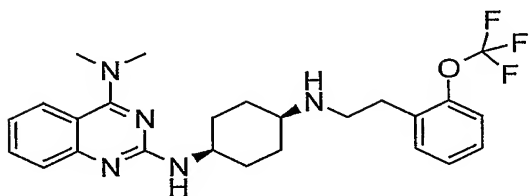
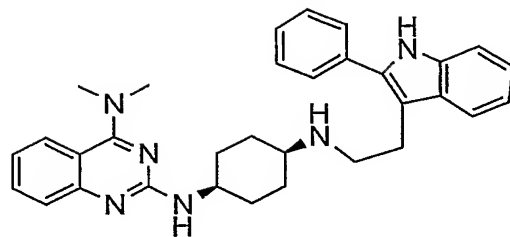
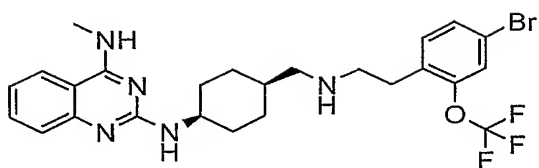


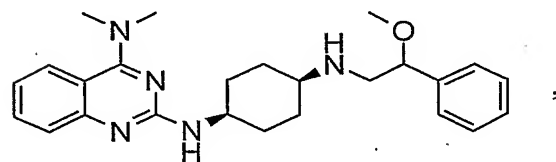
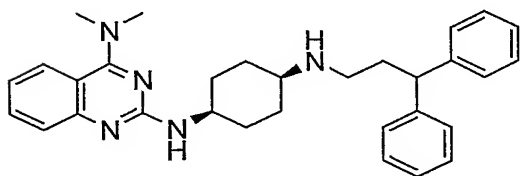
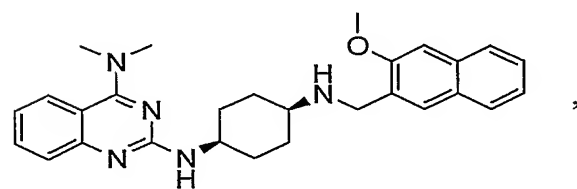
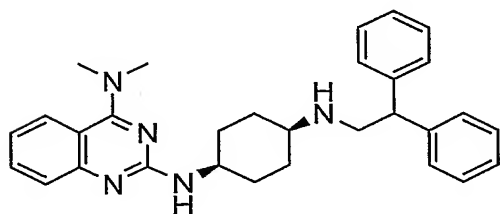
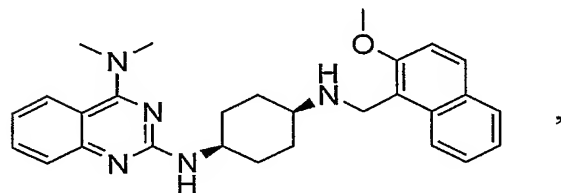
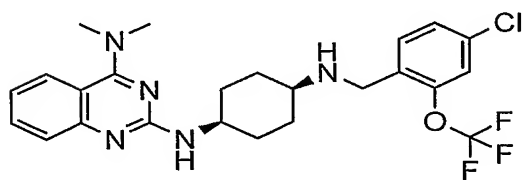
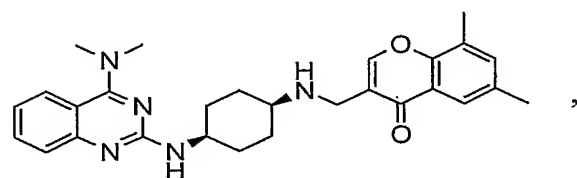
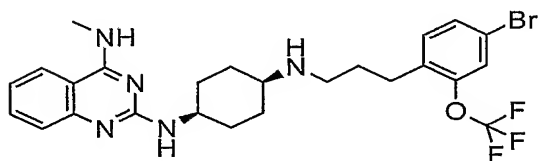
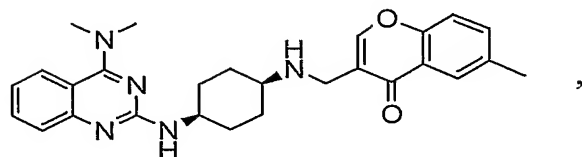
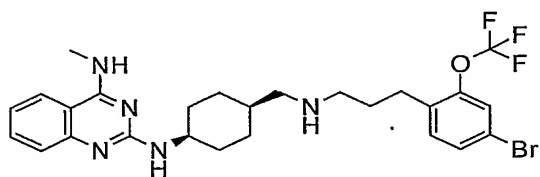
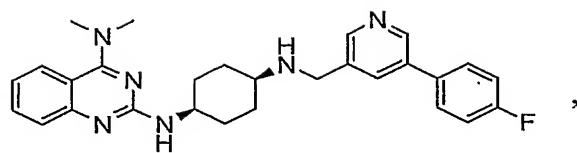
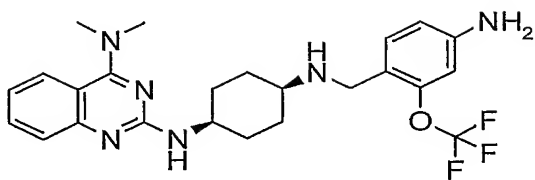
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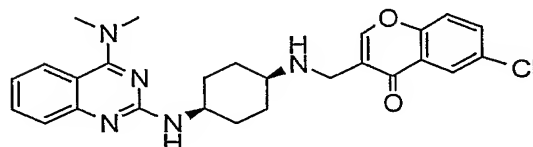
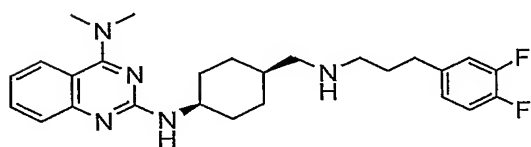
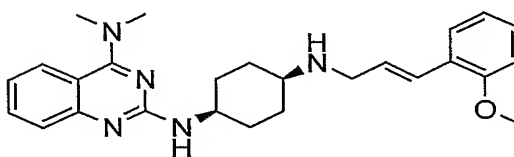
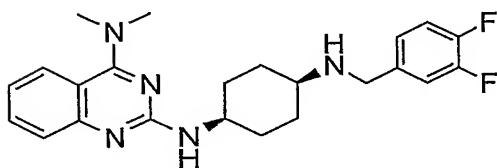
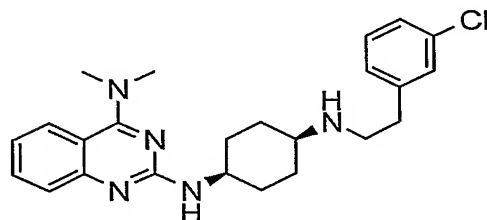
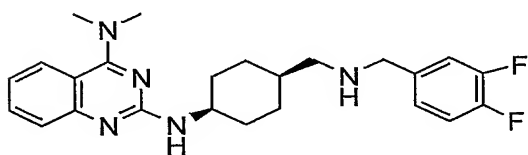
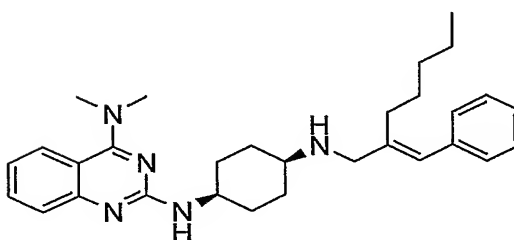
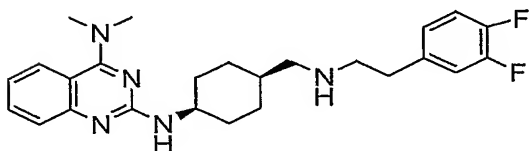
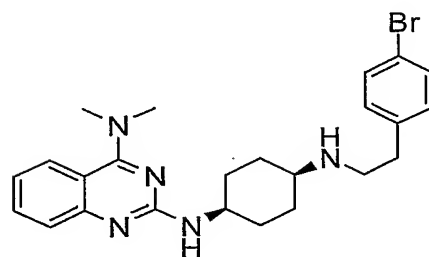
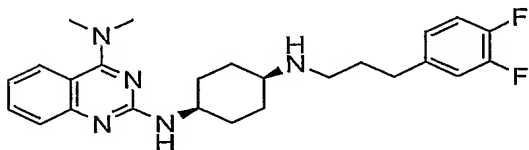
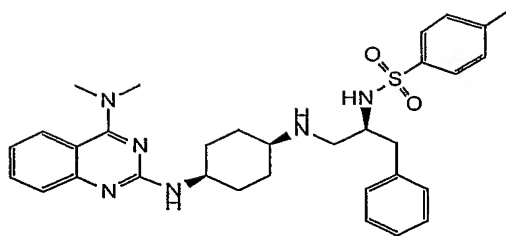
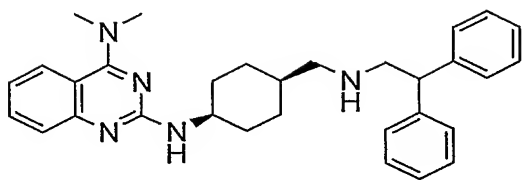


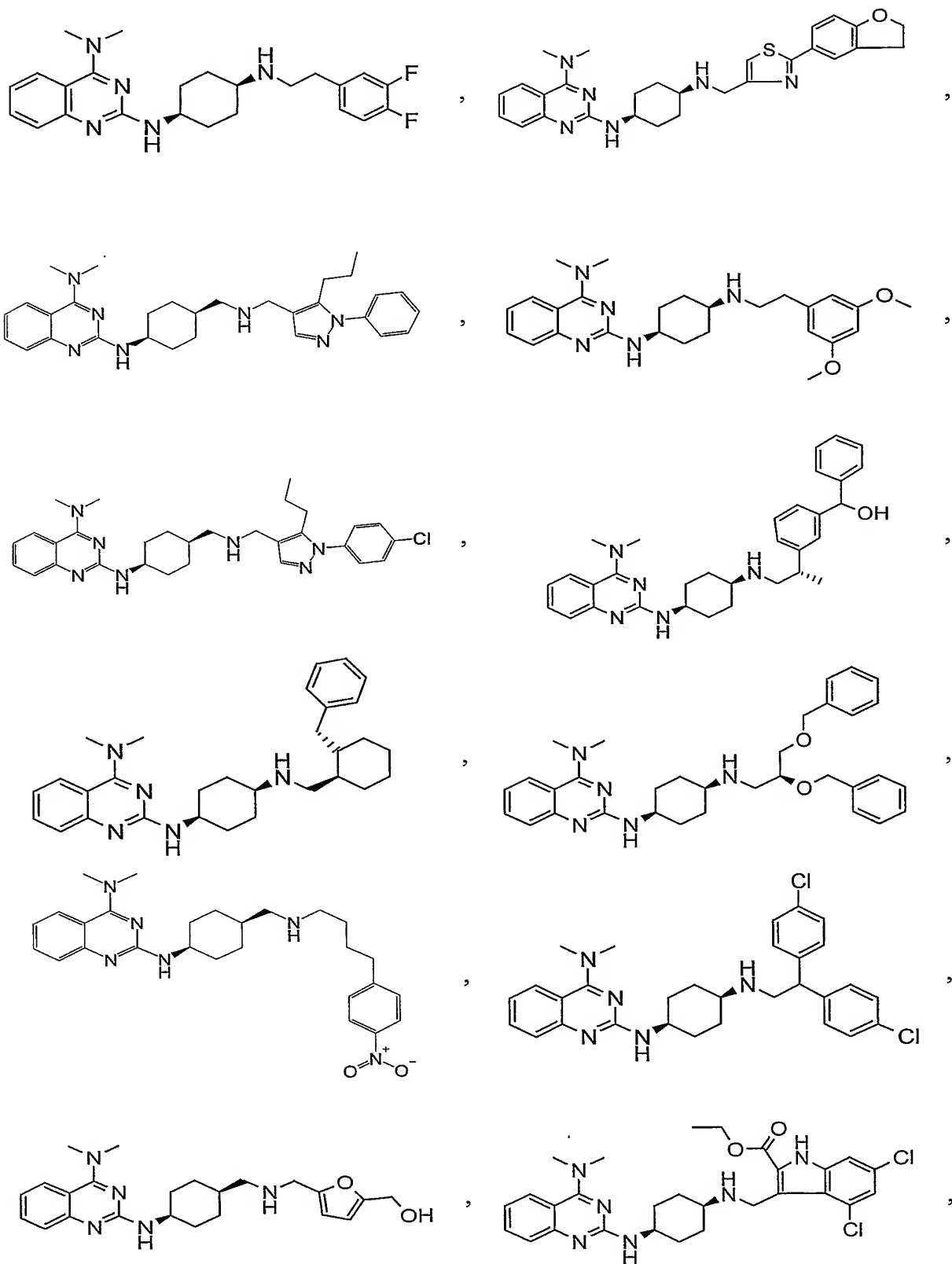
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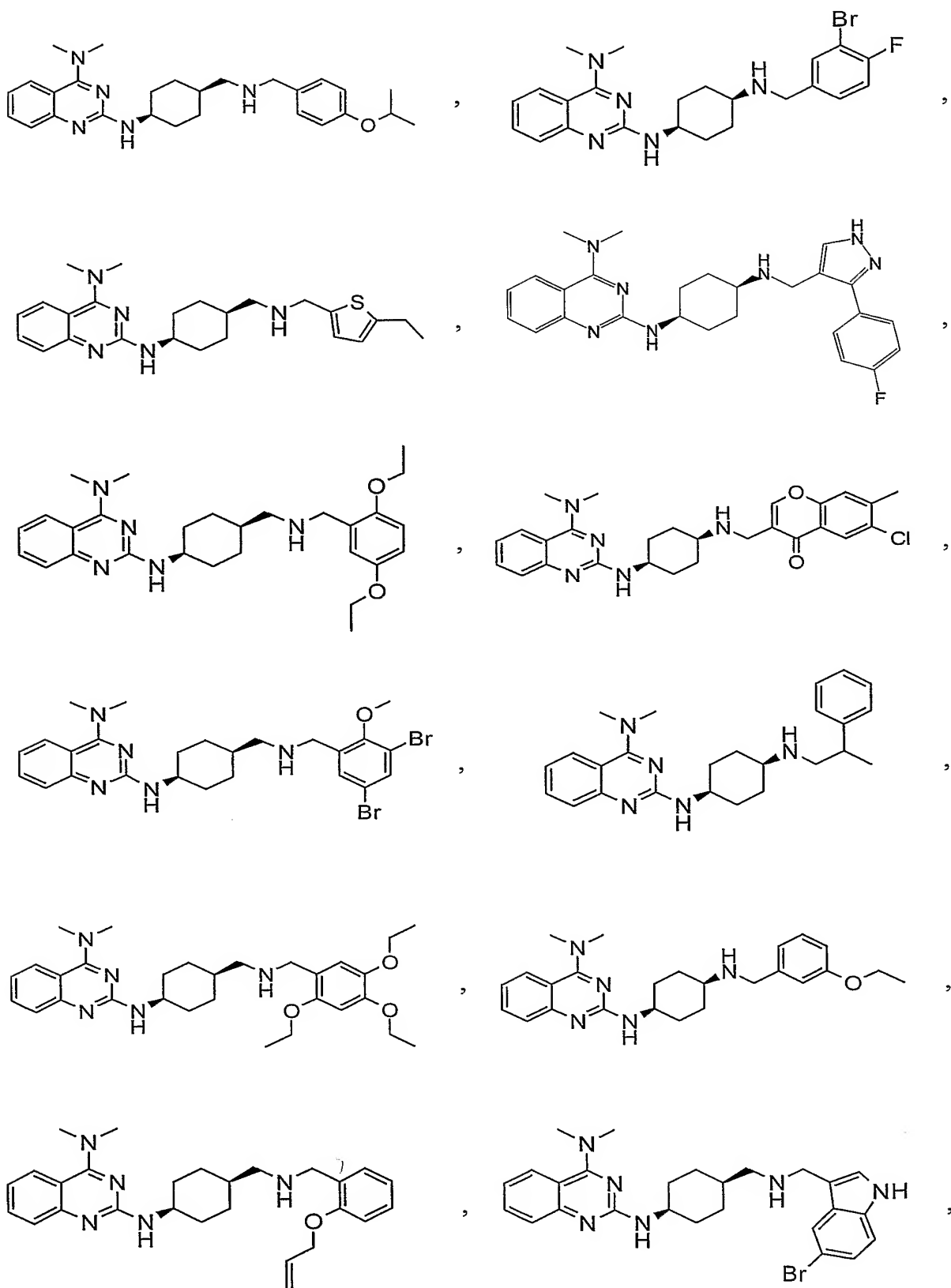


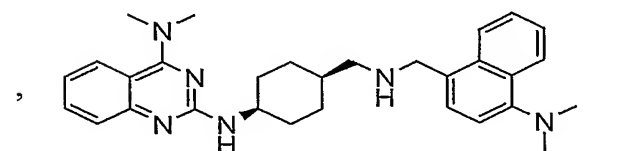
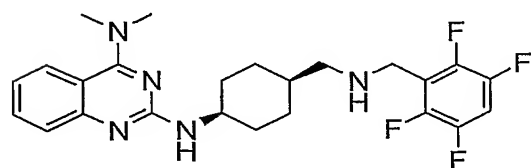
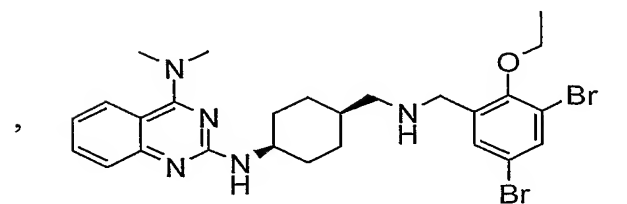
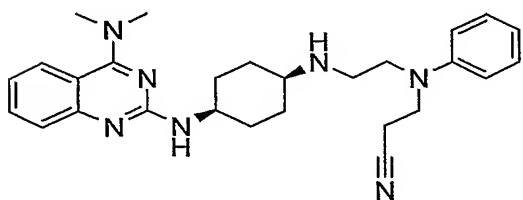
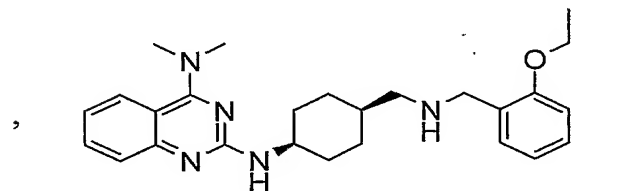
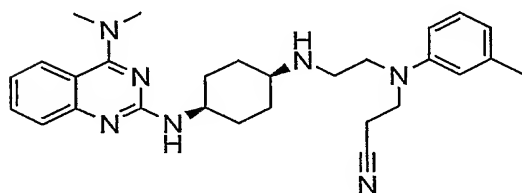
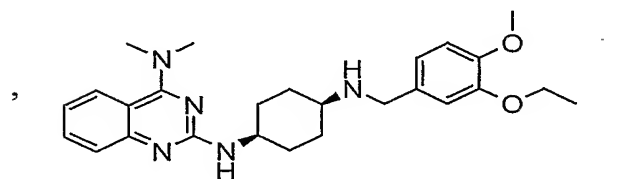
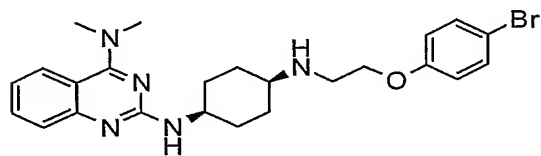
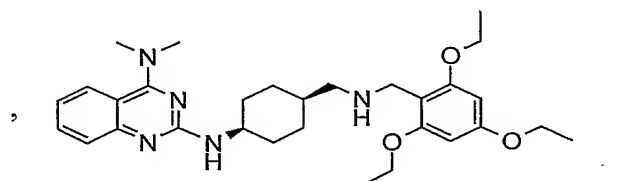
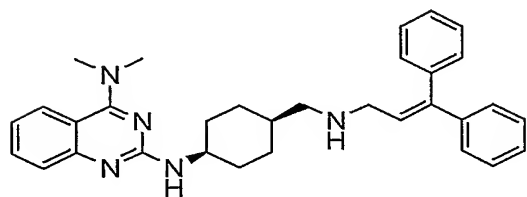
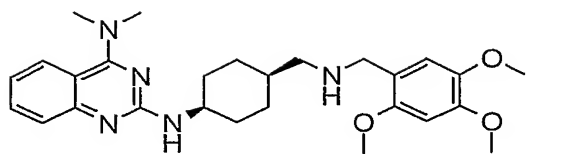
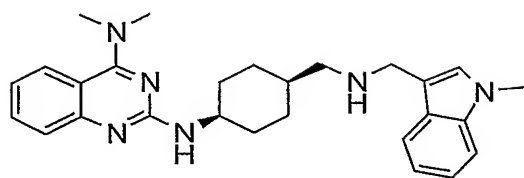


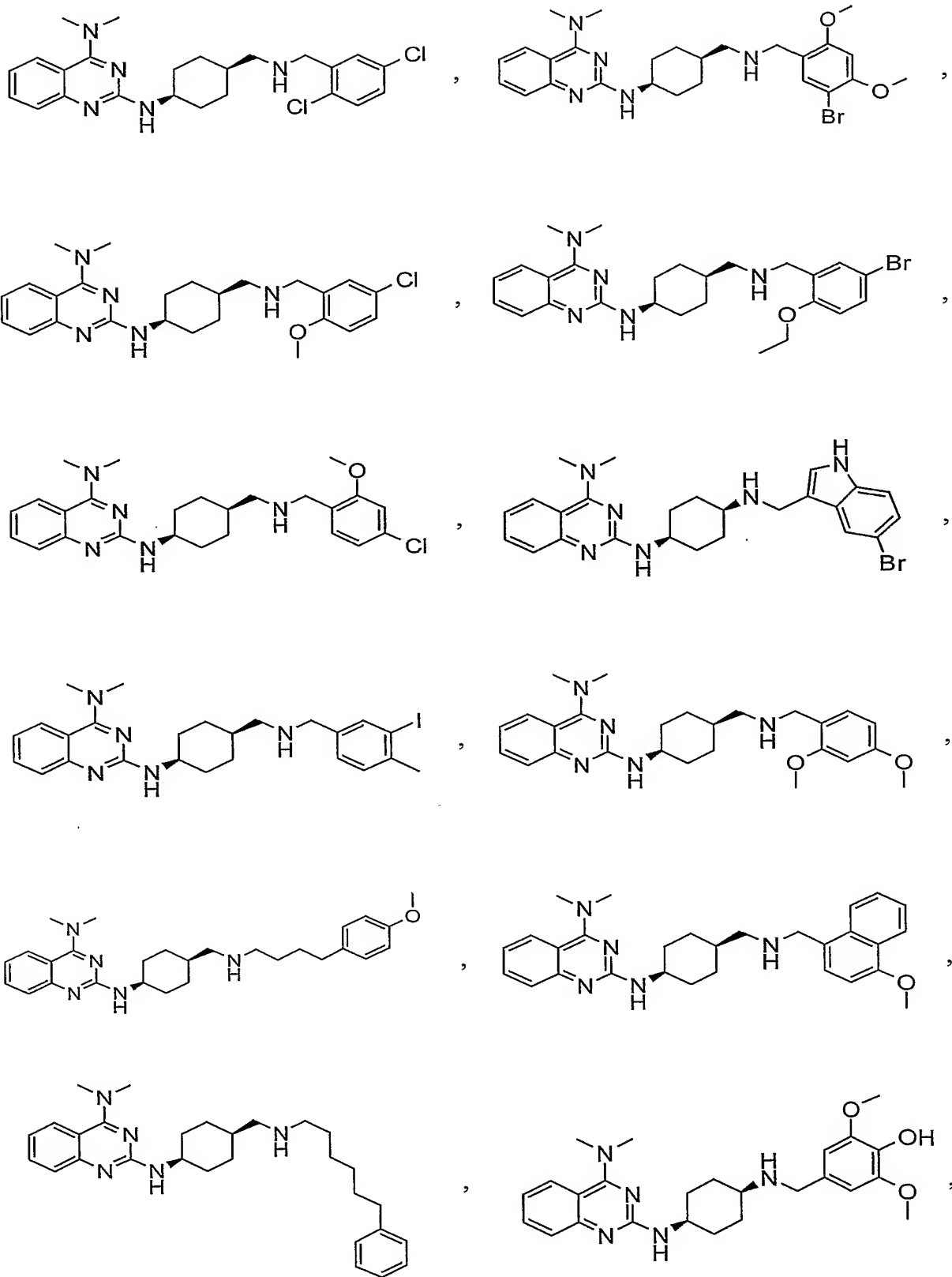


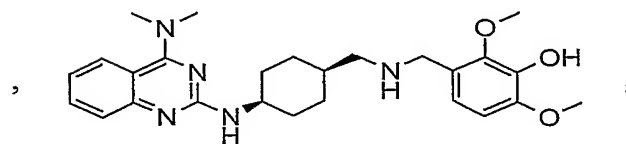
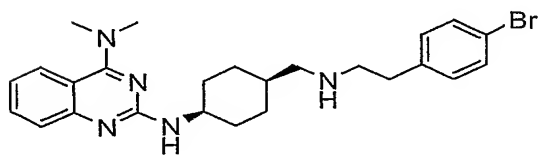
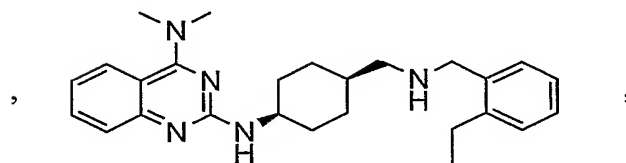
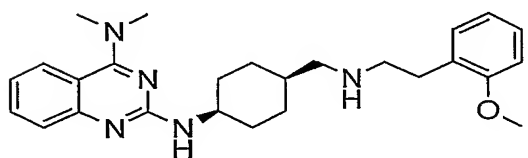
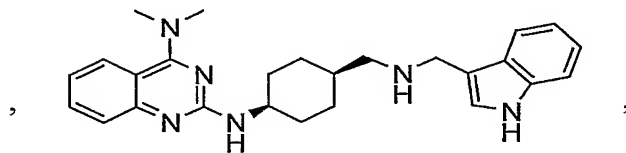
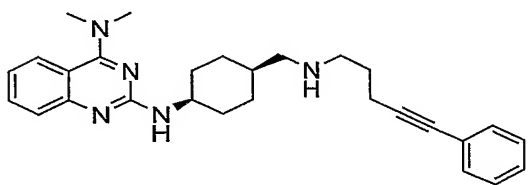
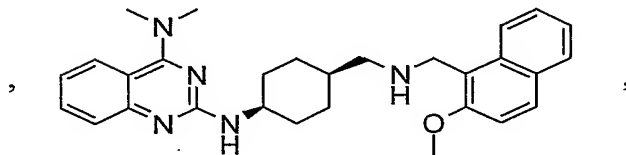
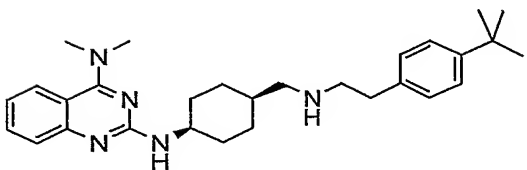
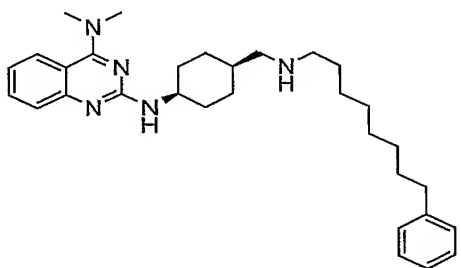
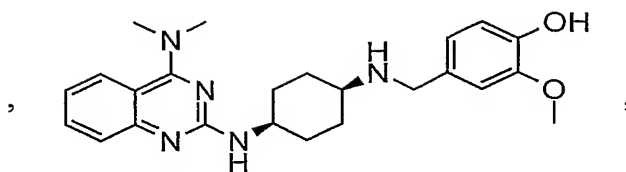
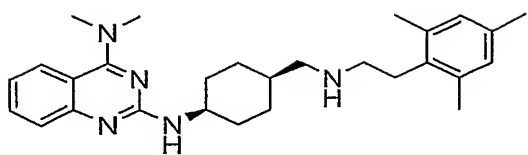


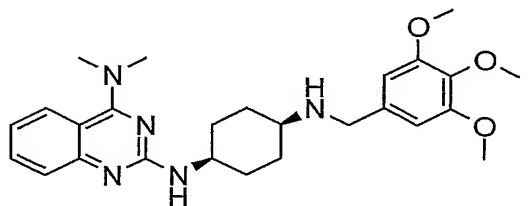
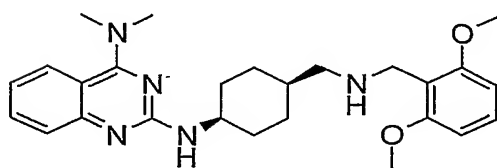
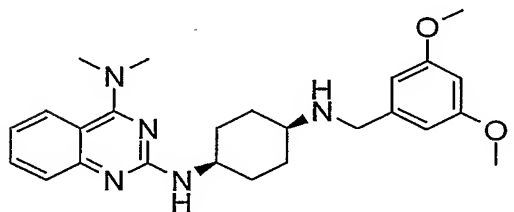
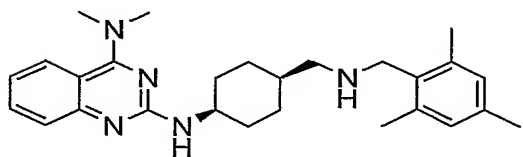
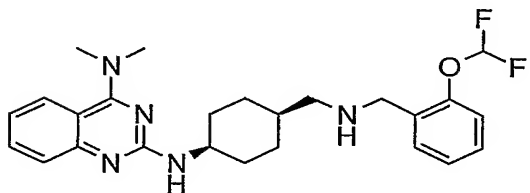
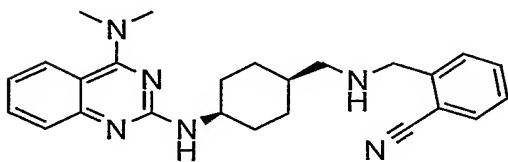
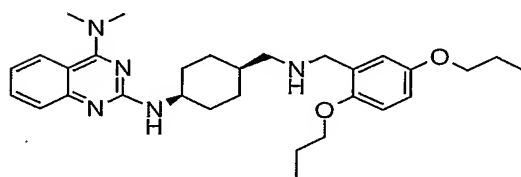
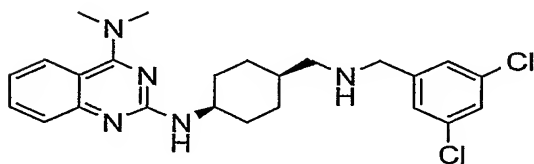
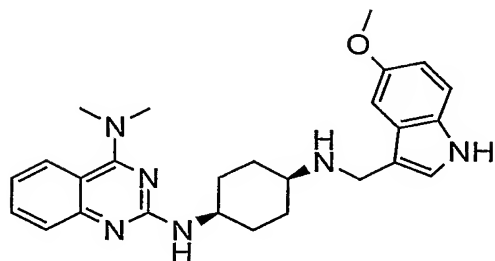
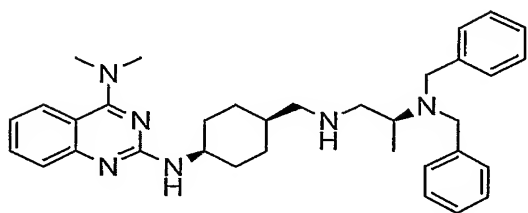
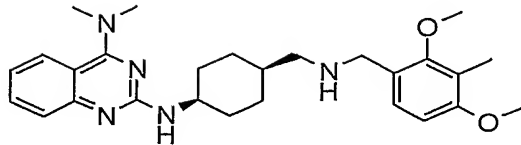
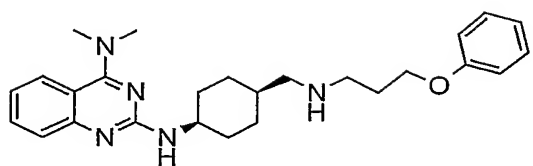


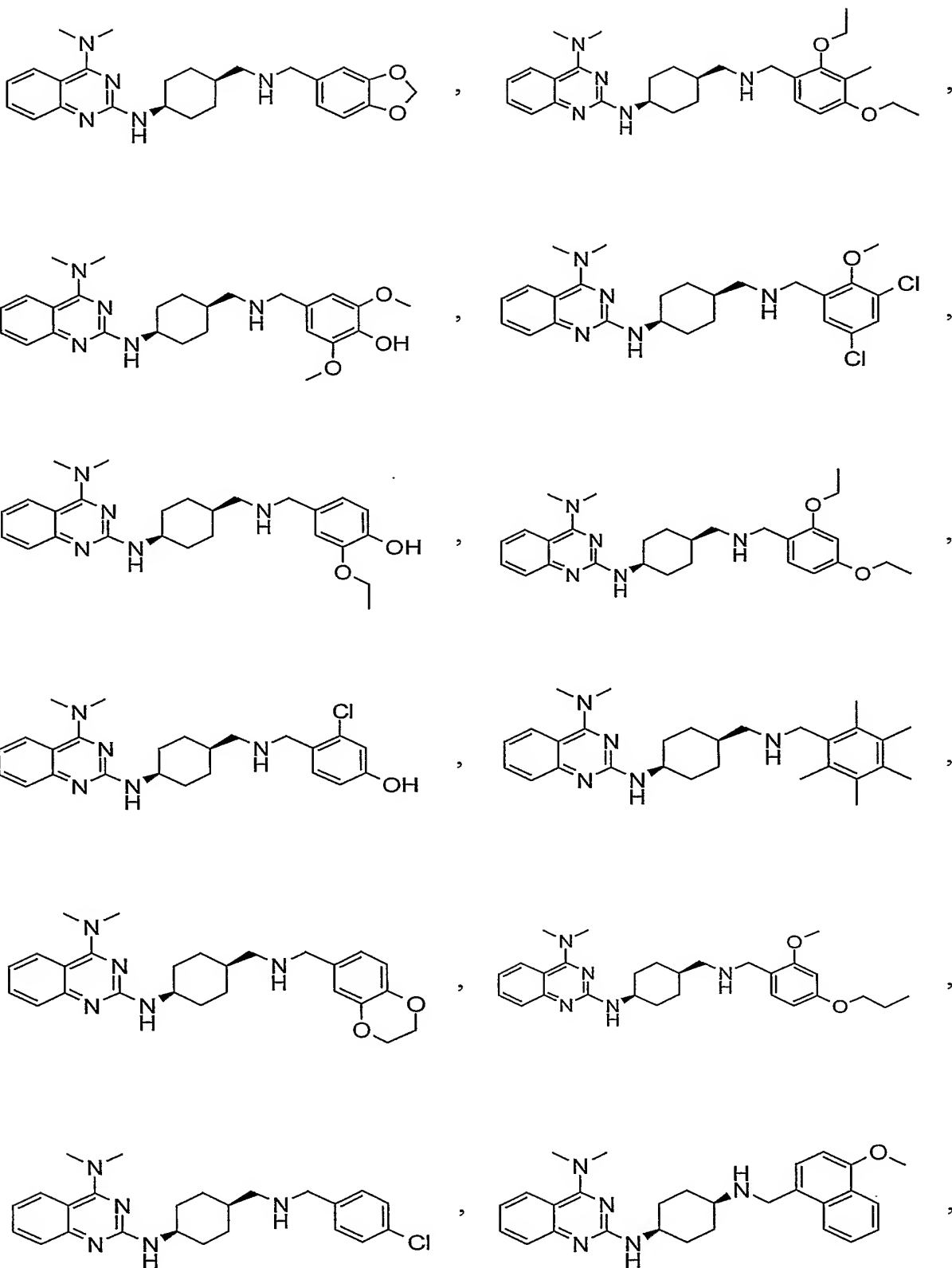


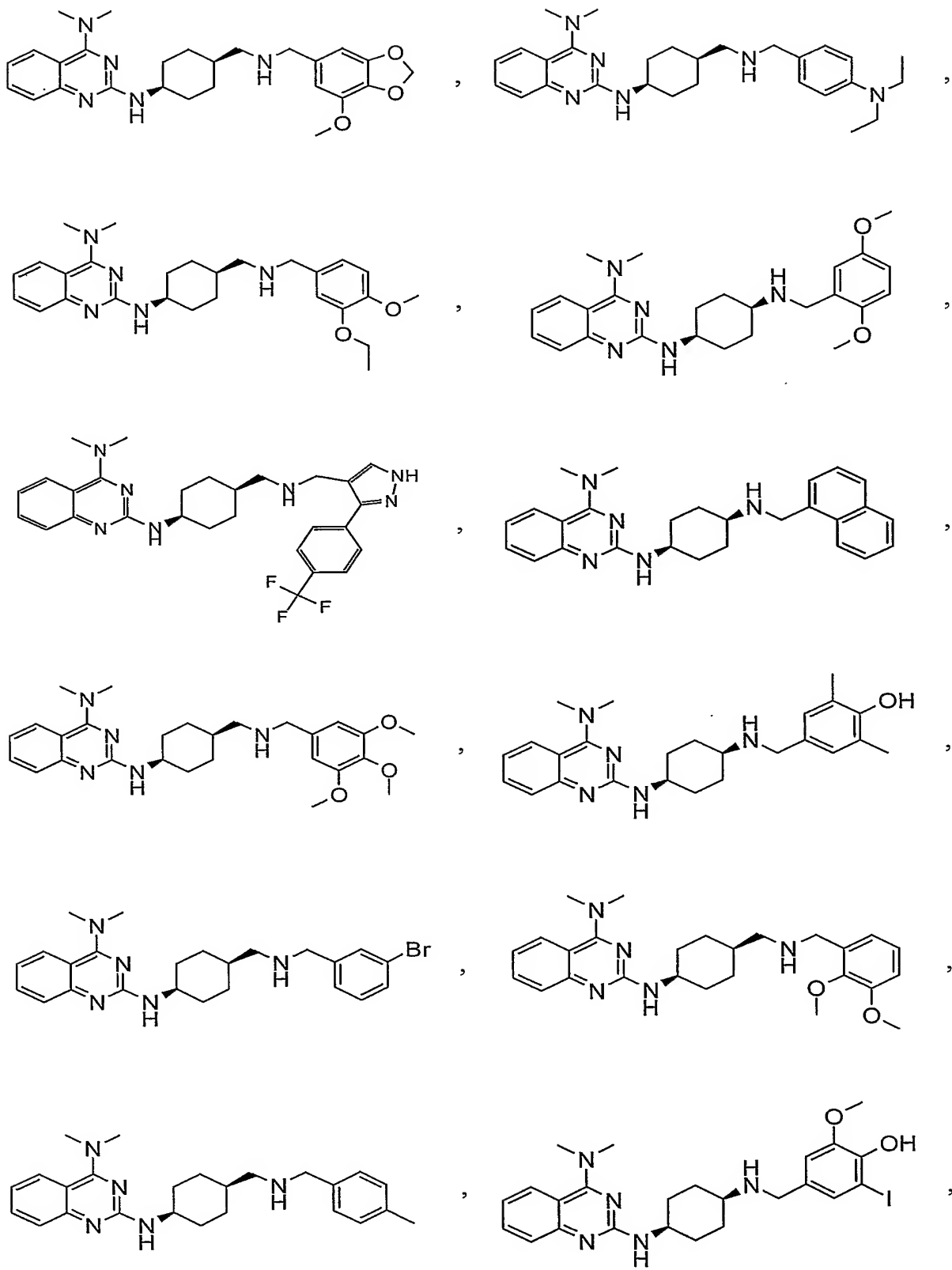


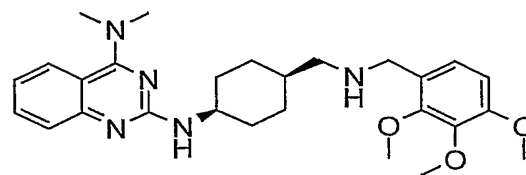
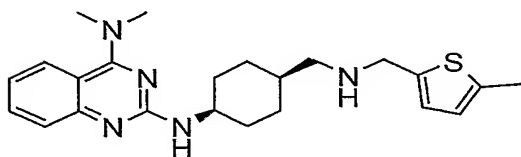
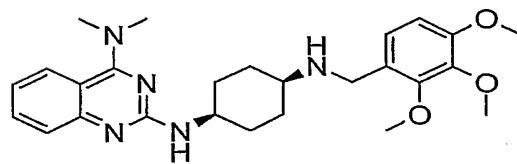
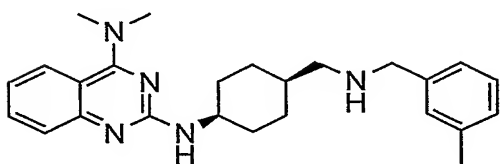
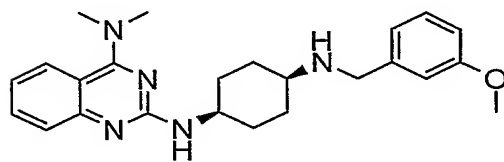
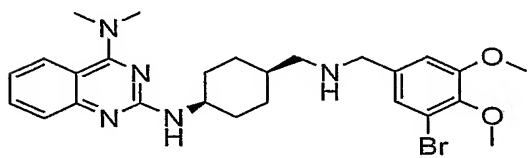
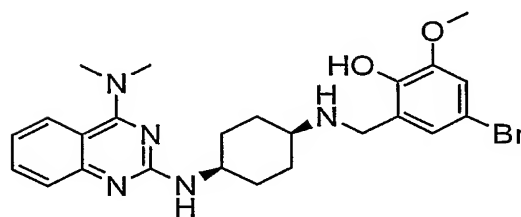
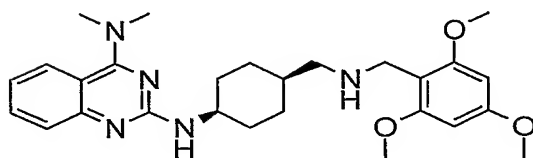
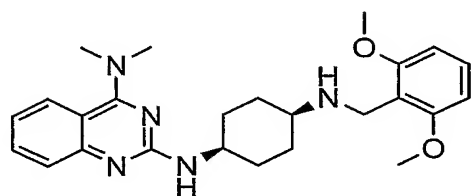
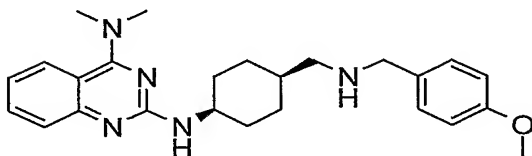
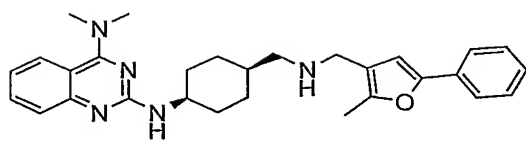
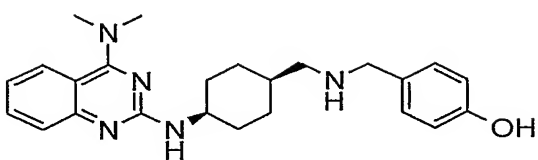


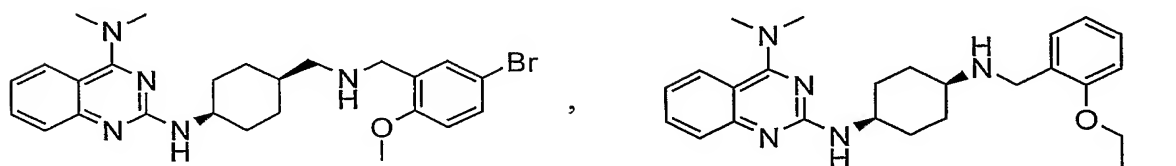
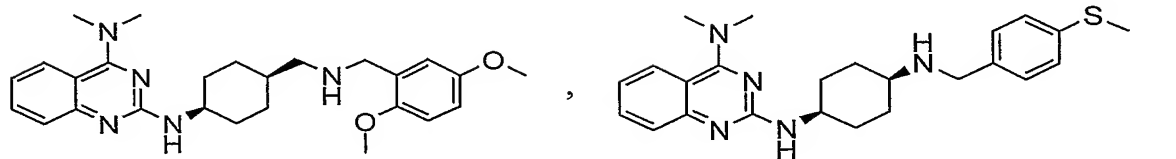
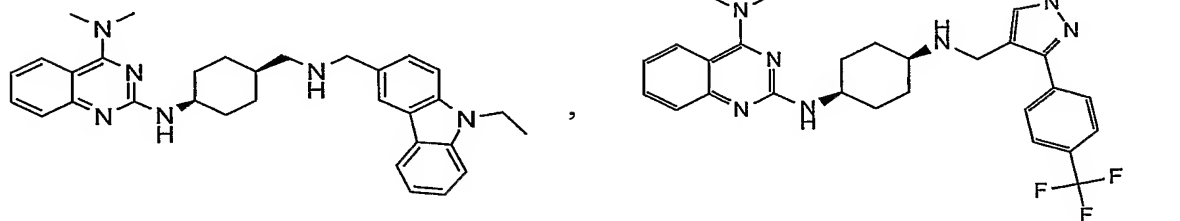
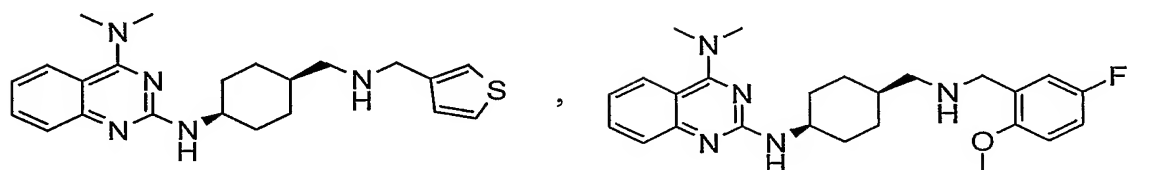
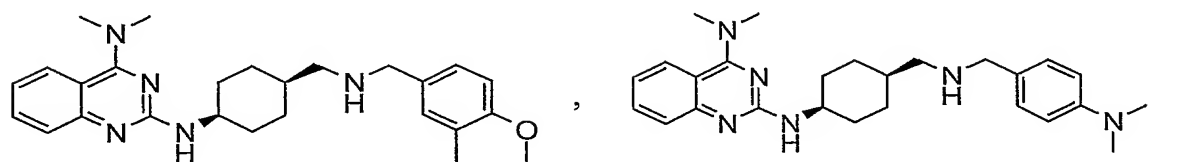
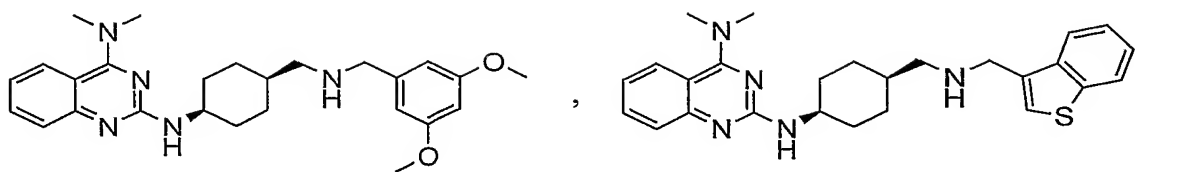


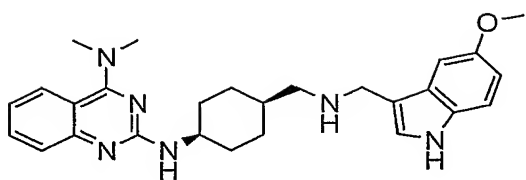




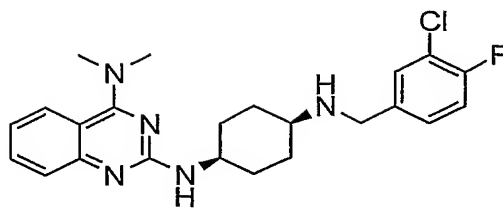




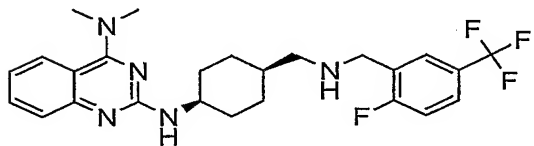




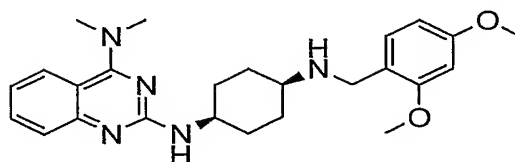
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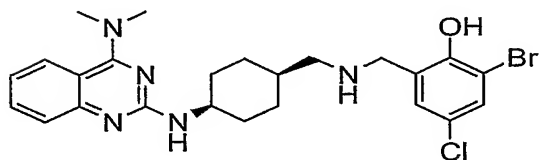
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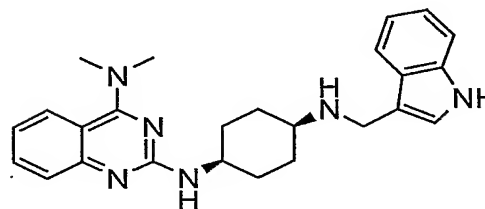
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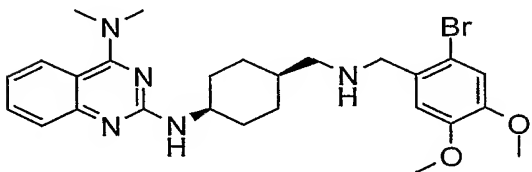
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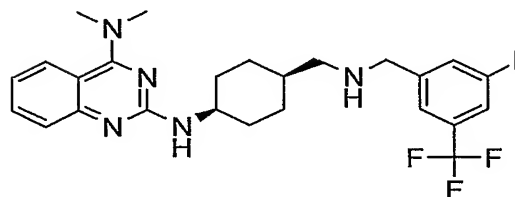
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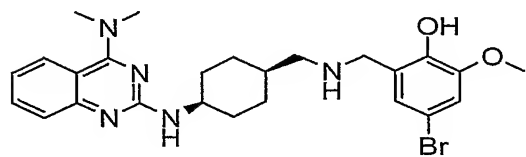
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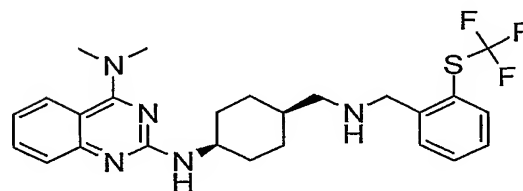
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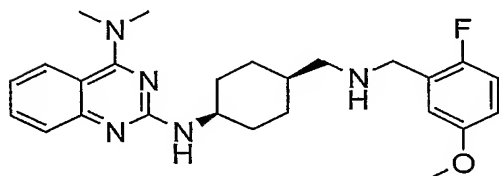
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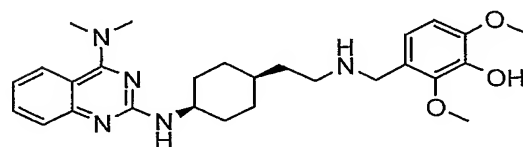
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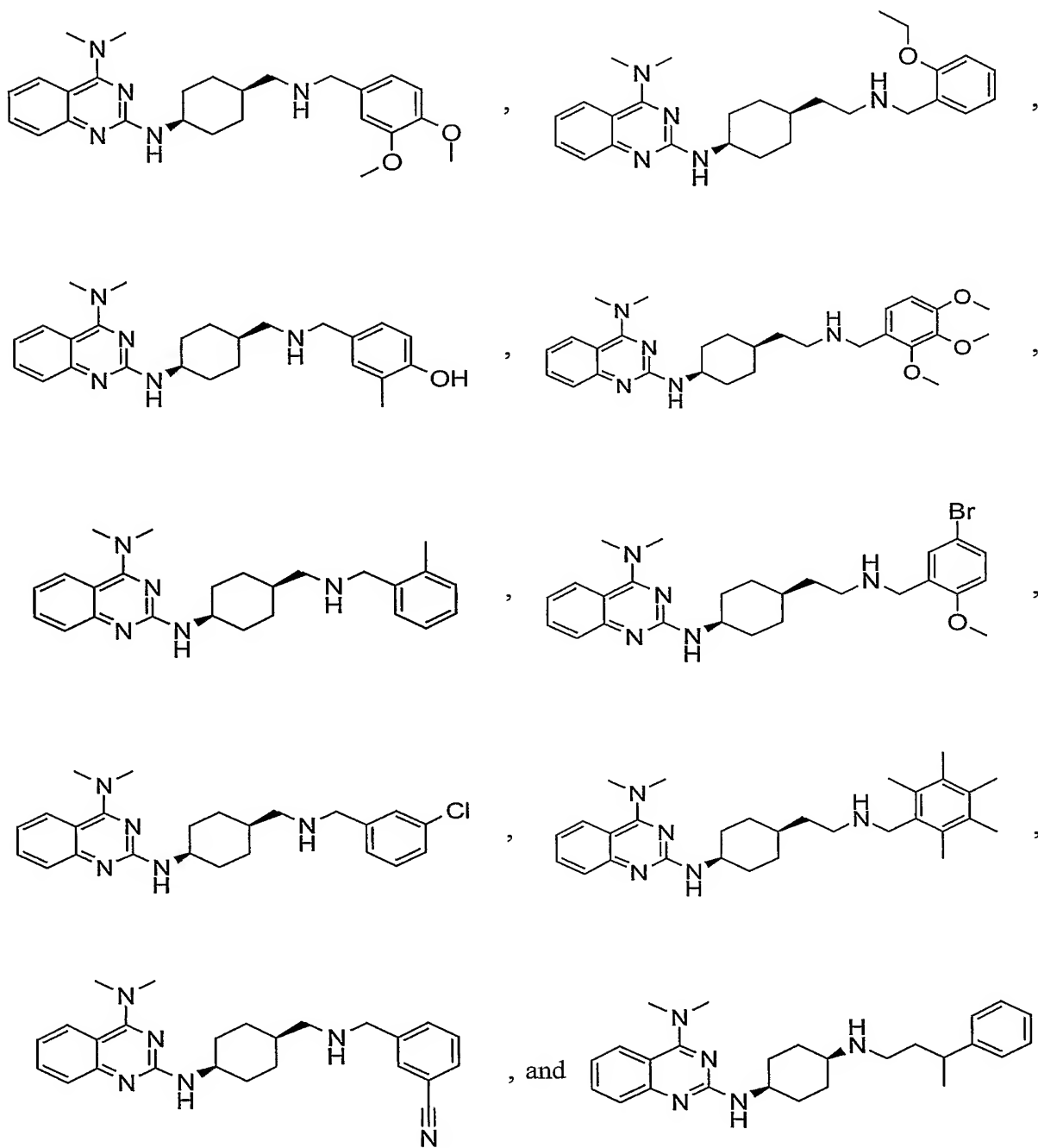
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,



; or, in case of, a salt thereof.

Preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₆ alkyl,

C₁-C₁₆ alkyl substituted by substituent(s) independently selected from

- halogen,
- carbocyclyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,

(ii) C₂-C₃ alkenyl,

C₂-C₃ alkenyl substituted by carbocyclic aryl,

(iii) carbocyclic aryl,

carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,
- cyano,
- nitro,
- C₁-C₅ alkyl,
- C₁-C₅ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - oxo,
 - C₂-C₃ alkenyl,
 - C₁-C₄ alkoxy,
 - C₁-C₄ alkoxy substituted by substituent(s) independently selected from
 - halogen,
 - heterocyclyl,
 - halogenated heterocyclyl,
 - carbocyclic aryloxy,
 - carbocyclic aryloxy substituted by substituent(s) independently selected from

- halogen,
- nitro,
- heterocycloxy,
- heterocycloxy substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- C₁-C₃ alkoxycarbonyl,
- mono- or di-C₁-C₄ alkylamino,
- C₁-C₃ alkylcarbonylamino,
- carbocyclic aryl diazo,
- carbocyclic aryl diazo substituted by mono- or di- C₁-C₃ alkylamino,
- C₁-C₃ alkylsulfonyl,
- carbocyclic aryl,
- (iv) heterocyclyl,
- or heterocyclyl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- C₁-C₃ alkyl substituted by substituent(s) independently selected from
- halogen,
- oxo,
- carbocyclic arylcarbonylamino,
- halogenated carbocyclic arylcarbonylamino,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- C₁-C₃ alkylcarbonylamino,
- carbocyclic arylsulfonyl,
- C₁-C₃ alkoxycarbonyl,

- carbocyclic aryl,
- halogenated carbocyclic aryl,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl;

R₂ is -NHNH₂, -NHNHBoc, -N(R_{2a})(R_{2b}), morpholino, 4-acetyl-piperazyl, or 4-phenyl-piperazyl;

wherein R_{2a} is H or C₁-C₃ alkyl;

R_{2b} is C₁-C₄ alkyl, C₁-C₄ alkyl substituted by substituent(s) independently selected from

- hydroxy,
- C₁-C₃ alkoxy,
- amino,
- NHBoc,
- C₃-C₆ cycloalkyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- SO₂NH₂,
- heterocyclyl,

C₃-C₆ cycloalkyl, carbocyclic aryl, carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,
- C₁-C₃ alkyl,
- C₁-C₃ alkoxy,

or a group of Formula IV;

wherein Boc is carbamic acid *tert*-butyl ester and R₃ is C₁-C₃ alkyl or C₁-C₃ alkyl substituted by substituent(s) independently selected from

- carbocyclic aryl,

- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by C₁-C₃ alkoxy;

L is selected from Formula V - XIX;

wherein R₄ is H or C₁-C₃ alkyl;

R₅ is H, C₁-C₃ alkyl, or C₁-C₃ alkyl substituted by a substituted carbocyclic aryl;

Y is -S(O)₂-;

wherein carbocyclic aryl is phenyl, naphthyl, or biphenyl;

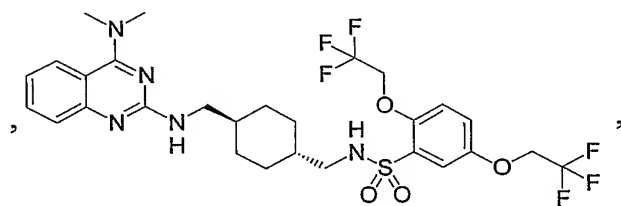
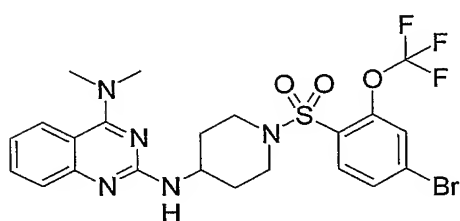
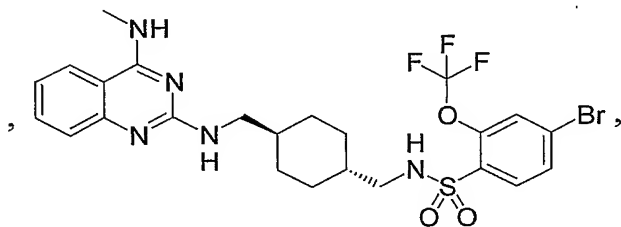
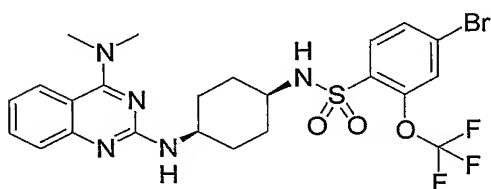
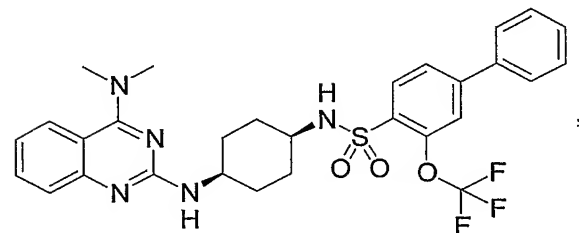
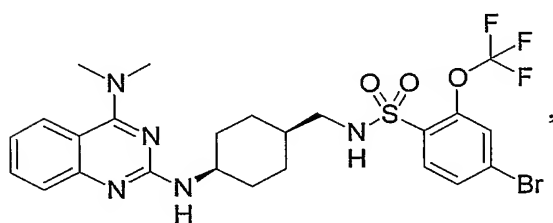
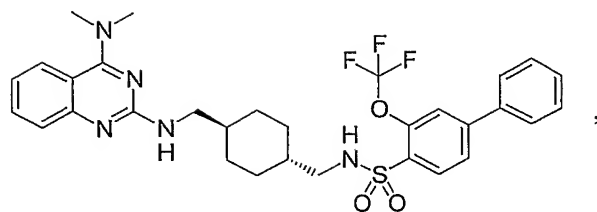
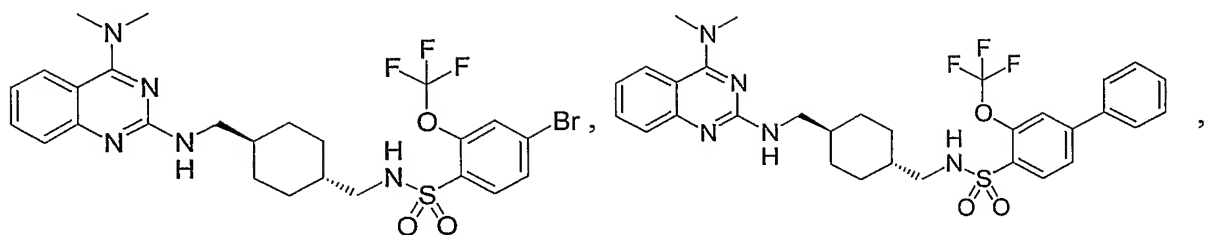
carbocyclyl is 7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptyl;

heterocyclyl is 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3-thiadiazolyl, 1*H*-pyrrolyl,

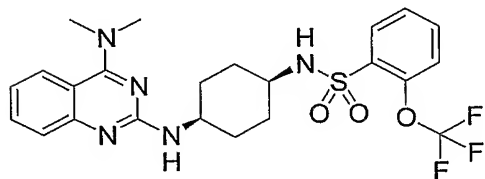
benzo[2,1,3]oxadiazolyl, benzo[b]thienyl, furyl, imidazolyl, isoxazolyl, pyrazolyl, pyridyl, quinolyl, thiazolyl, or thienyl;

halogen is fluoro, chloro, bromo, or iodo.

The following compounds are specially preferred;



and



; or, in case of, a salt thereof.

Preferred compounds of this invention are those compounds of Formula I wherein,
Q is Formula II;
R₁ is selected from H, -CO₂^tBu, or -CO₂Bn (Bn is a benzyl group);
R₂ is methylamino or dimethylamino;
L is selected from Formula XX - XXII;
Y is a single bond;
or a salt thereof.

Also provided in accordance with the present invention are methods of modulating G-protein receptor SLC-1 comprising contacting the SLC-1 receptor with a compound of the invention.

The present invention further provides pharmaceutical compositions containing MCH receptor antagonists of the invention.

Brief Description of the Figures

Figure 1 provides an illustration of IP₃ production from several non-endogenous, constitutively activated version of MCH receptor as compared with the endogenous version of this receptor.

Detailed Description

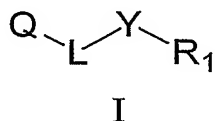
The present invention relates to MCH receptor antagonist compounds, and methods of modulating MCH receptors by contacting the receptors with one or more compounds of the invention.

The term “antagonist” is intended to mean moieties that competitively bind to the receptor at the same site as agonists (for example, the endogenous ligand), but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. Antagonists do not diminish the baseline intracellular response in the absence of an agonist or partial agonist. As used herein, the term “agonist” is intended to mean moieties that activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes. In the context of the present invention, a pharmaceutical composition comprising a MCH receptor antagonist of the invention can be utilized for modulating the activity of the MCH receptor,

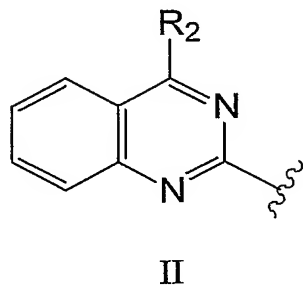
decreasing body weight and/or affecting metabolism such that the recipient loses weight and/or maintains weight. Such pharmaceutical compositions can be used in the context of disorders and/or diseases where weight gain is a component of the disease and/or disorder such as, for example, obesity.

As used herein, the term "contact" or "contacting" shall mean bringing the indicated moieties together, whether in an in vitro system or an in vivo system. Thus, "contacting" an MCH receptor with a compound of the invention includes the administration of a compound of the invention to an animal having an MCH receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or more purified preparation containing an MCH receptor.

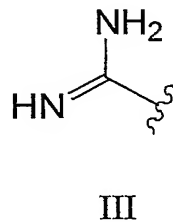
Compounds of the invention include those having Formula I, shown below:



wherein Q can be either Formula II or III:



or



R₁ represents

(i) C₁-C₁₆ alkyl,

C₁-C₁₆ alkyl substituted by substituent(s) independently selected from

•halogen,

•hydroxy,

•oxo,

•C₁-C₃ alkoxy,

•C₁-C₃ alkoxy substituted by substituent(s) independently selected from

••carbocyclic aryl,

- heterocyclyl,
- heterocyclyl substituted by C₁-C₃ alkyl,
- C₁-C₃ alkylcarbonyloxy,
- carbocyclyloxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by substituent(s) independently selected from
- halogen,
- nitro,
- carbocyclic aryl,
- carbocyclic aryl substituted by C₁-C₃ alkoxy,
- C₁-C₄ alkyl,
- C₁-C₄ alkyl substituted by substituent(s) independently selected from
- oxo,
- mono- or di-C₁-C₃ alkylamino,
- mono- or di-C₁-C₃ alkylamino substituted by carbocyclic aryl,
- mono- or di-C₁-C₃ alkylamino substituted by halogenated carbocyclic aryl,
- carbocyclic arylcarbonylamino,
- halogenated carbocyclic arylcarbonylamino,
- heterocyclyloxy,
- heterocyclyloxy substituted by C₁-C₃ alkyl,
- substituted heterocyclyl-ethylideneaminooxy,
- C₁-C₃ alkoxycarbonyl,
- C₁-C₃ alkoxycarbonyl substituted by carbocyclic aryl,
- mono- or di-C₁-C₃ alkylaminocarbonyl,
- mono- or di-C₁-C₃ alkylamino,
- mono- or di-C₁-C₃ alkylamino substituted by substituent(s) independently selected from
- cyano,
- carbocyclic aryl,
- heterocyclyl,
- mono- or di-carbocyclic arylamino,
- mono- or di-carbocyclic arylamino substituted by substituent(s) independently selected from

- hydroxy,
- C₁-C₃ alkyl,
- C₁-C₃ alkylcarbonylamino,
- C₁-C₃ alkylcarbonylamino substituted by substituent(s) independently selected from
- C₁-C₃ alkylcarbonylamino,
- carbocyclic arylcarbonylamino,
- heterocyclyl,
- C₁-C₄ alkoxy carbonylamino,
- heterocyclyl carbonylamino,
- carbocyclic arylsulfonylamino,
- carbocyclic arylsulfonylamino substituted by substituent(s) independently selected from
- nitro,
- C₁-C₃ alkyl,
- mono- or di-C₁-C₃ alkylamino,
- C₁-C₃ alkylthio,
- C₁-C₃ alkylthio substituted by substituent(s) independently selected from
- mono- or di-carbocyclic arylaminocarbonyl,
- halogenated mono- or di-carbocyclic arylaminocarbonyl,
- mono- or di-carbocyclic arylamino,
- halogenated mono- or di-carbocyclic arylamino,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkoxy,
- carbocyclic arylthio,
- carbocyclic arylthio substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- carbocyclic arylsulfonyl,
- halogenated carbocyclic arylsulfonyl,
- heterocyclylthio,
- heterocyclylthio substituted by substituent(s) independently selected from

- nitro,
- C₁-C₃ alkyl,
- C₃-C₆ cycloalkyl,
- C₃-C₆ cycloalkyl substituted by C₁-C₃ alkyl,
- C₃-C₆ cycloalkenyl,
- carbocyclyl,
- carbocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - C₂-C₃ alkenyl,
 - C₂-C₃ alkenyl substituted by carbocyclic aryl,
 - C₂-C₃ alkenyl substituted by carbocyclic aryl substituted C₁-C₃ alkylsulfinyl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - oxo,
 - carbocyclic aryl,
 - heterocyclyl,
 - mono- or di-carbocyclic arylamino,
 - mono- or di-carbocyclic arylamino substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,

- halogenated C₁-C₃ alkoxy,
- C₁-C₄ alkoxy,
- C₁-C₄ alkoxy substituted by substituent(s) independently selected from
 - halogen,
 - carbocyclic aryl,
 - carbocyclic aryloxy,
 - C₁-C₃ alkoxycarbonyl,
 - C₁-C₃ alkylcarbonyloxy,
 - mono- or di-C₁-C₃ alkylamino,
 - mono- or di-carbocyclic arylamino,
 - halogenated mono- or di-carbocyclic arylamino,
 - mono- or di-carbocyclic arylaminocarbonyl,
 - mono- or di-carbocyclic arylaminocarbonyl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - halogenated C₁-C₃ alkoxy,
 - mercapto,
 - C₁-C₃ alkylthio,
 - halogenated C₁-C₃ alkylthio,
 - C₁-C₃ alkylsulfonyl,
 - C₃-C₆ cycloalkyl,
 - carbocyclic aryl,
 - heterocyclyl,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - hydroxy,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkyl substituted by carbocyclic aryl,
 - C₁-C₃ alkoxy,

- C₁-C₃ alkoxy substituted by carbocyclic aryl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- (ii) C₂-C₈ alkenyl,
C₂-C₈ alkenyl substituted by substituent(s) independently selected from
 - halogen,
 - oxo,
 - C₁-C₃ alkoxy,
 - C₁-C₃ alkoxy substituted by carbocyclic aryl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - nitro,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - halogenated C₁-C₃ alkoxy,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - hydroxy,
 - nitro,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
- (iii) C₂-C₄ alkynyl,
C₂-C₄ alkynyl substituted by carbocyclic aryl,
- (iv) C₃-C₆ cycloalkyl,
C₃-C₆ cycloalkyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,
 - C₁-C₃ alkyl substituted by substituent(s) independently selected from
 - hydroxy,
 - oxo,

- carbocyclic aryl,
- mono- or di-C₁-C₃ alkylamino,
- mono- or di-C₁-C₃ alkylamino substituted by carbocyclic aryl,
- carbocyclic arylcarbonylamino,
- carbocyclic aryl,
- (v) C₃-C₆ cycloalkyl,
- C₃-C₆ cycloalkyl substituted by C₁-C₃ alkyl,
- (vi) carbocyclyl,
- carbocyclyl substituted by substituent(s) independently selected from
 - hydroxy,
 - nitro,
- (vii) carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - nitro,
 - C₁-C₉ alkyl,
 - C₁-C₉ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - oxo,
 - C₁-C₃ alkoxy,
 - carbocyclic aryloxy,
 - mono- or di-C₁-C₃ alkylamino-N-oxy,
 - mono- or di-C₁-C₃ alkylamino,
 - mono- or di-C₁-C₃ alkylamino substituted by carbocyclic aryl,
 - mono- or di-carbocyclic arylamino,
 - carbocyclylimino,
 - carbocyclylimino substituted by carbocyclic aryl,
 - mono- or di-carbocyclic arylamino,
 - mono- or di-carbocyclic arylamino substituted by C₁-C₃ alkoxy,

- mono- or di-carbocyclic arylaminocarbonyl,
- mono- or di-carbocyclic arylaminocarbonyl substituted by C₁-C₃ alkoxy,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
- heterocyclyl,
- heterocyclyl substituted by C₁-C₃ alkyl,
- C₂-C₃ alkenyl,
- C₂-C₃ alkenyl substituted by carbocyclic aryl,
- C₁-C₉ alkoxy,
- C₁-C₉ alkoxy substituted by substituent(s) independently selected from
 - hydroxy,
 - halogen,
 - carboxy,
 - mono- or di-C₁-C₃ alkylamino,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
- C₂-C₃ alkenyloxy,
- C₁-C₃ alkylcarbonyloxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by substituent(s) independently selected from
 - halogen,

- nitro,
- C₁-C₄ alkyl,
- halogenated C₁-C₄ alkyl,
- C₁-C₃ alkoxy,
- heterocyclyloxy,
- heterocyclyloxy substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- (carbocyclic aryl)S(O)₂O,
- carboxy,
- C₁-C₃ alkoxycarbonyl,
- mono- or di-C₁-C₃ alkylaminocarbonyl,
- mono- or di-C₁-C₃ alkylaminocarbonyl substituted by carbocyclic aryl,
- mono- or di-carbocyclic arylaminocarbonyl,
- mono- or di-carbocyclic arylaminocarbonyl substituted by C₁-C₃ alkyl,
- amino,
- mono- or di-C₁-C₄ alkylamino,
- mono- or di-C₁-C₄ alkylamino substituted by cyano,
- mono- or di-carbocyclic arylamino,
- C₁-C₃ alkynylcarbonylamino,
- C₁-C₃ alkynylcarbonylamino substituted by carbocyclic aryl,
- carbocyclic arylsulfonylamino,
- carbocyclic arylsulfonylamino substituted by C₁-C₃ alkyl,
- (carbocyclic aryl)NHC(O)NH,
- (carbocyclic aryl)NHC(O)NH substituted by C₁-C₃ alkoxy,
- (carbocyclic aryl)NHC(O)NH substituted by halogenated C₁-C₃ alkoxy,
- carbocyclic aryl diazo,
- carbocyclic aryl diazo substituted by mono- or di- C₁-C₃ alkylamino,
- C₁-C₃ alkylthio,
- halogenated C₁-C₃ alkylthio,
- carbocyclic arylthio,

- carbocyclic arylthio substituted by substituent(s) independently selected from
 - halogen,
 - cyano,
 - C₁-C₃ alkyl,
- heterocyclylthio,
- C₁-C₃ alkylsulfonyl,
- mono- or di-C₁-C₃ alkylaminosulfonyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - C₁-C₇ alkyl,
 - halogenated C₁-C₇ alkyl,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
- (viii) heterocyclyl,
- or heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - nitro,
 - C₁-C₄ alkyl,
- C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - oxo,
 - C₁-C₃ alkylcarbonyloxy,
 - carbocyclic arylcarbonylamino,
 - halogenated carbocyclic arylcarbonylamino,
 - C₁-C₃ alkoxycarbonyl,
 - C₁-C₃ alkylthio,

- C₁-C₃ alkylthio substituted by carbocyclic aryl,
- C₁-C₃ alkylthio substituted by halogenated carbocyclic aryl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- C₁-C₃ alkoxy substituted by carbocyclic aryl,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by substituent(s) independently selected from
 - halogen,
- C₁-C₃ alkyl,
- mono- or di-C₁-C₃ alkylamino,
- C₁-C₄ alkylcarbonylamino,
- C₁-C₃ alkylthio,
- C₁-C₃ alkenylthio,
- carbocyclic arylthio,
- halogenated carbocyclic arylthio,
- carbocyclic arylthio substituted by C₁-C₃ alkoxycarbonyl,
- heterocyclylthio,
- heterocyclylthio substituted by C₁-C₃ alkyl,
- C₁-C₃ alkylsulfonyl,
- carbocyclic arylsulfonyl,
- halogenated carbocyclic arylsulfonyl,
- carbocyclic arylsulfonyl substituted by C₁-C₄ alkyl,
- C₁-C₃ alkoxycarbonyl,
- carbocyclic aryl,

•carbocyclic aryl substituted by substituent(s) independently selected from

••halogen,

••nitro,

••C₁-C₃ alkyl,

••halogenated C₁-C₃ alkyl,

••C₁-C₃ alkoxy,

••halogenated C₁-C₃ alkoxy,

•heterocyclyl,

•heterocyclyl substituted by substituent(s) independently selected from

••halogen,

••C₁-C₃ alkyl,

••halogenated C₁-C₃ alkyl,

••C₁-C₃ alkoxy,

••C₁-C₃ alkoxycarbonyl;

R₂ is -NHNH₂, -NHNHBoc, -N(R_{2a})(R_{2b}), morpholino, 4-acetyl-piperazyl, or 4-phenyl-piperazyl;

wherein R_{2a} is H or C₁-C₃ alkyl;

R_{2b} is C₁-C₄ alkyl, C₁-C₄ alkyl substituted by substituent(s) independently selected from

•hydroxy,

•C₁-C₃ alkoxy,

•amino,

•-NHBoc,

•C₃-C₆ cycloalkyl,

•carbocyclic aryl,

•carbocyclic aryl substituted by substituent(s) independently selected from

••halogen,

••C₁-C₃ alkyl,

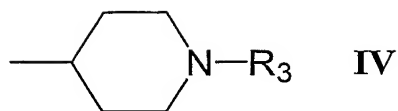
••C₁-C₃ alkoxy,

••-SO₂NH₂,

•heterocyclyl,

C₃-C₆ cycloalkyl, carbocyclic aryl, carbocyclic aryl substituted by substituent(s) independently selected from

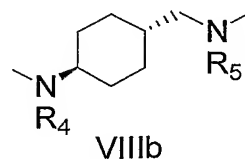
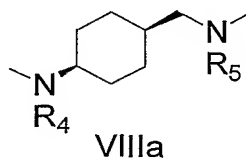
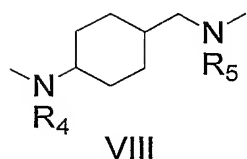
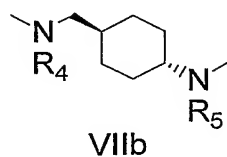
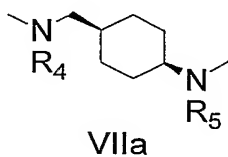
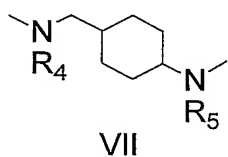
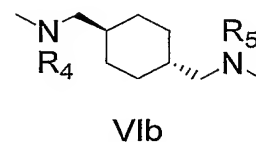
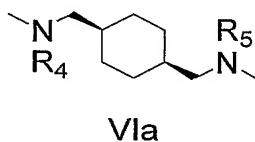
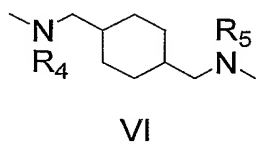
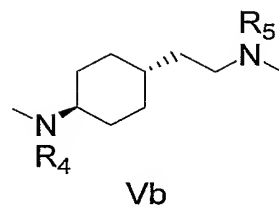
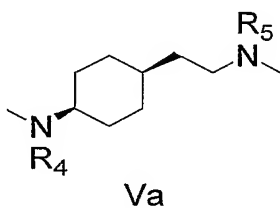
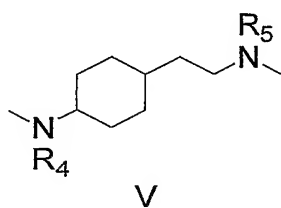
- halogen,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
- or a group of Formula IV;

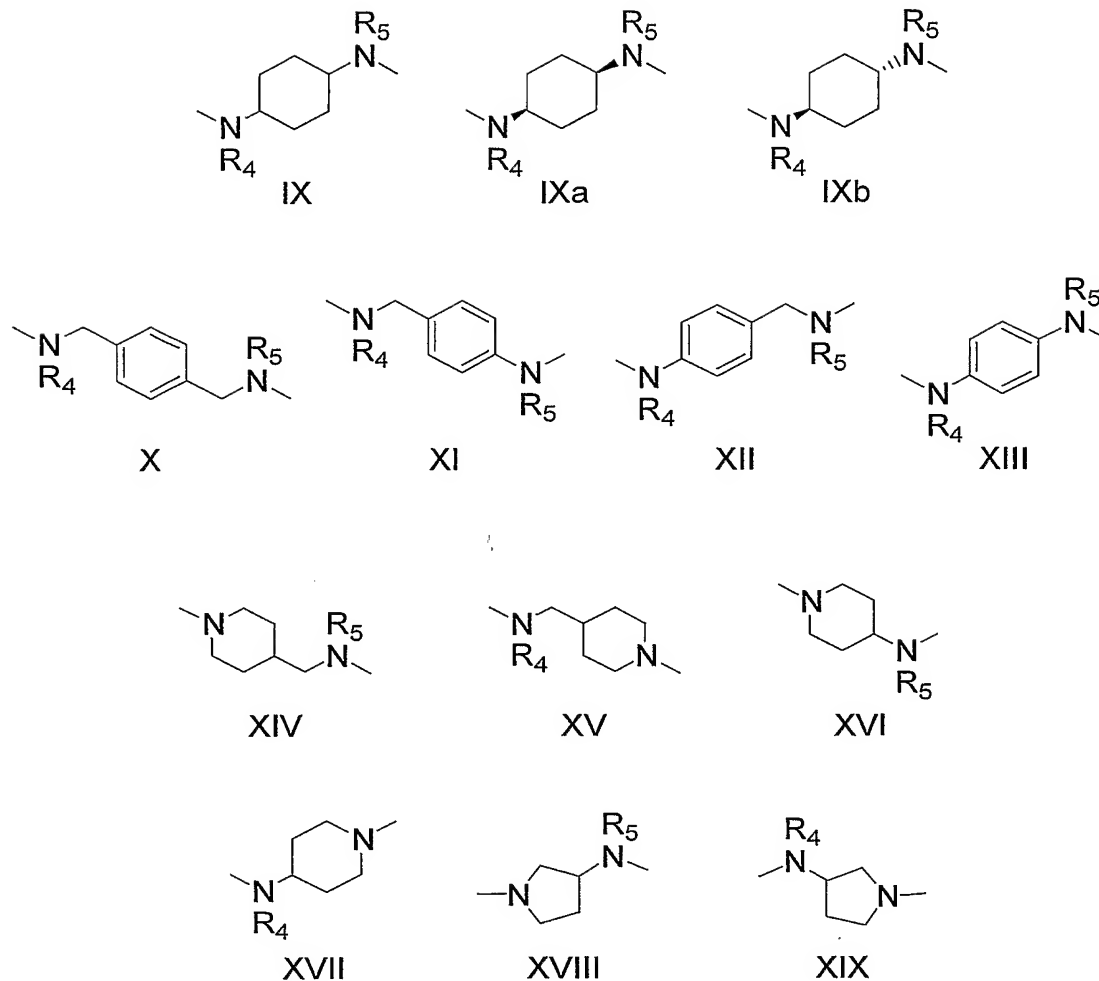


wherein Boc is carbamic acid *tert*-butyl ester and R₃ is C₁-C₃ alkyl or C₁-C₃ alkyl substituted by substituent(s) independently selected from

- carbocyclic aryl,
- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by C₁-C₃ alkoxy;

L is selected from Formula V - XIX;





wherein R₄ is H or C₁-C₃ alkyl;

R₅ is H, C₁-C₃ alkyl, or C₁-C₃ alkyl substituted by a substituted carbocyclic aryl;

Y is -S(O)₂-, -C(O)-, or -(CH₂)_m;

m is 0 or 1;

wherein carbocyclic aryl is phenyl, naphthyl, anthranyl, biphenyl, or phenanthryl;

carbocyclyl is 10,11-dihydro-5-oxo-dibenzo[a,d]cycloheptyl, 1-oxo-indanyl, 7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptyl, 9H-fluorenyl, 9-oxo-fluorenyl, acenaphthyl, anthraquinonyl, C-fluoren-9-ylidene, indanyl, indenyl, 1,2,3,4-tetrahydro-naphthyl, or bicyclo[2.2.1]heptenyl;

heterocyclyl is 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3-thiadiazolyl, 1,2,3-triazolyl,

1,2-dihydro-3-oxo-pyrazolyl, 1,3,4-thiadiazolyl, 1,3-dioxo-isoindolyl, 1,3-dioxolanyl, 1*H*-indolyl, 1*H*-pyrrolo[2,3-*c*]pyridyl, 1*H*-pyrrolyl, 1-oxo-3*H*-isobenzofuranyl, 2,2',5',2"-terthiophenyl, 2,2'-bithiophenyl, 2,3-dihydro-1-oxo-isoindolyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2,3-dihydro-benzofuryl, 2,4-dihydro-3-oxo-pyrazolyl, 2*H*-benzopyranyl, 2-oxo-benzopyranyl, 2-oxo-pyrrolidinyl, 3,4-dihydro-2*H*-benzo[1,4]oxazinyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepinyl, 4*H*-benzo[1,3]dioxinyl, 4*H*-benzopyranyl, 4-oxo-1,5,6,7-tetrahydro-indolyl, 4-oxo-3,4-dihydro-phthalazinyl, 4-oxo-benzopyranyl, 9,10,10-trioxo-thioxanthenyl, 9*H*-carbazolyl, 9*H*-xanthenyl, azetidiny, benzimidazolyl, benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[*b*]thienyl, benzofuryl, benzothiazolyl, cinnolyl, furyl, imidazo[2,1-*b*]thiazolyl, imidazolyl, isoxazolyl, morpholino, morpholinyl, oxazolyl, oxolanyl, piperazyl, piperidyl, piridyl, pyrazolo[5,1-*b*]thiazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolidyl, quinolyl, quinoxalyl, thiazolidyl, thiazolyl, thienyl, thiolanyl, 2,3-dihydro-benzofuryl, tetrahydro-thienyl, or benzofuranyl;

halogen is fluoro, chloro, bromo, or iodo.

Preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₀ alkyl,

C₁-C₁₀ alkyl substituted by substituent(s) independently selected from

•halogen,

•oxo,

•C₁-C₃ alkoxy,

•C₁-C₃ alkoxy substituted by carbocyclic aryl,

•C₁-C₃ alkylcarbonyloxy,

•carbocyclyloxy,

•carbocyclic aryloxy,

•carbocyclic aryloxy substituted by substituent(s) independently selected from

••halogen,

••nitro,

••C₁-C₄ alkyl,

••C₁-C₄ alkyl substituted by substituent(s) independently selected from

- oxo,
- carbocyclic arylcarbonylamino,
- halogenated carbocyclic arylcarbonylamino,
- heterocycloxy,
- heterocycloxy substituted by C₁-C₃ alkyl,
- substituted heterocyclyl-ethylideneaminooxy,
- C₁-C₃ alkoxycarbonyl,
- C₁-C₃ alkoxycarbonyl substituted by carbocyclic aryl,
- mono- or di-C₁-C₃ alkylaminocarbonyl,
- mono- or di-carbocyclic arylamino,
- mono- or di-carbocyclic arylamino substituted by hydroxy,
- C₁-C₃ alkylcarbonylamino,
- C₁-C₃ alkylcarbonylamino substituted by substituent(s) independently selected from
- C₁-C₃ alkylcarbonylamino,
- carbocyclic arylcarbonylamino,
- heterocyclyl,
- C₁-C₄ alkoxycarbonylamino,
- heterocyclyl carbonylamino,
- carbocyclic arylsulfonylamino,
- carbocyclic arylsulfonylamino substituted by substituent(s) independently selected from
- nitro,
- C₁-C₃ alkyl,
- mono- or di-C₁-C₃ alkylamino,
- C₁-C₃ alkylthio,
- C₁-C₃ alkylthio substituted by substituent(s) independently selected from
- mono- or di-carbocyclic arylaminocarbonyl,
- halogenated mono- or di-carbocyclic arylaminocarbonyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkoxy,
- carbocyclic arylthio,

- carbocyclic arylthio substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
- carbocyclic arylsulfonyl,
- halogenated carbocyclic arylsulfonyl,
- heterocyclylthio,
- heterocyclylthio substituted by substituent(s) independently selected from
 - nitro,
 - C₁-C₃ alkyl,
 - C₃-C₆ cycloalkyl,
 - C₃-C₆ cycloalkyl substituted by C₁-C₃ alkyl,
 - C₃-C₆ cycloalkenyl,
- carbocyclyl,
- carbocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - C₂-C₃ alkenyl,
 - C₂-C₃ alkenyl substituted by carbocyclic aryl,
 - C₂-C₃ alkenyl substituted by carbocyclic aryl substituted C₁-C₃ alkylsulfinyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - oxo,
 - carbocyclic aryl,
 - heterocyclyl,
 - C₁-C₄ alkoxy,
 - C₁-C₄ alkoxy substituted by substituent(s) independently selected from

- halogen,
- carbocyclic aryl,
- carbocyclic aryloxy,
- C₁-C₃ alkylcarbonyloxy,
- mono- or di-carbocyclic arylamino,
- halogenated mono- or di-carbocyclic arylamino,
- mono- or di-carbocyclic arylaminocarbonyl,
- mono- or di-carbocyclic arylaminocarbonyl substituted by substituent(s) independently selected from
- halogen,
- nitro,
- C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- halogenated C₁-C₃ alkoxy,
- mercapto,
- C₁-C₃ alkylthio,
- halogenated C₁-C₃ alkylthio,
- C₁-C₃ alkylsulfonyl,
- C₃-C₆ cycloalkyl,
- carbocyclic aryl,
- heterocyclyl,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- hydroxy,
- C₁-C₃ alkyl,
- C₁-C₃ alkyl substituted by carbocyclic aryl,
- C₁-C₃ alkoxy,
- C₁-C₃ alkoxy substituted by carbocyclic aryl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- (ii) C₂-C₆ alkenyl,
- C₂-C₆ alkenyl substituted by substituent(s) independently selected from

- oxo,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - halogenated C₁-C₃ alkoxy,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
 - hydroxy,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
- (iii) C₃-C₆ cycloalkyl,
- C₃-C₆ cycloalkyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,
 - C₁-C₃ alkyl substituted by substituent(s) independently selected from
 - oxo,
 - carbocyclic aryl,
 - carbocyclic arylcarbonylamino,
 - carbocyclic aryl,
- (iv) carbocyclyl,
- carbocyclyl substituted by nitro,
- (v) carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - nitro,
 - C₁-C₉ alkyl,
 - C₁-C₉ alkyl substituted by substituent(s) independently selected from

- halogen,
- oxo,
- carbocyclic aryloxy,
- carbocyclylimino,
- carbocyclylimino substituted by carbocyclic aryl,
- mono- or di-carbocyclic arylaminocarbonyl,
- mono- or di-carbocyclic arylaminocarbonyl substituted by C₁-C₃ alkoxy,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl,
 - heterocyclyl,
 - heterocyclyl substituted by C₁-C₃ alkyl,
 - C₁-C₇ alkoxy,
 - C₁-C₇ alkoxy substituted by substituent(s) independently selected from
 - halogen,
 - carbocyclic aryl,
 - C₁-C₃ alkylcarbonyloxy,
 - carbocyclic aryloxy,
 - carbocyclic aryloxy substituted by C₁-C₃ alkoxy,
 - C₁-C₃ alkoxycarbonyl,
 - mono- or di-C₁-C₃ alkylaminocarbonyl,
 - mono- or di-C₁-C₃ alkylaminocarbonyl substituted by carbocyclic aryl,
 - mono- or di-carbocyclic arylaminocarbonyl,
 - mono- or di-carbocyclic arylaminocarbonyl substituted by C₁-C₃ alkyl,
 - amino,
 - mono- or di-C₁-C₃ alkylamino,
 - C₁-C₃ alkynylcarbonylamino,
 - C₁-C₃ alkynylcarbonylamino substituted by carbocyclic aryl,
 - carbocyclic arylsulfonylamino,
 - carbocyclic arylsulfonylamino substituted by C₁-C₃ alkyl,

- (carbocyclic aryl)NHC(O)NH,
- (carbocyclic aryl)NHC(O)NH substituted by C₁-C₃ alkoxy,
- (carbocyclic aryl)NHC(O)NH substituted by halogenated C₁-C₃ alkoxy,
- C₁-C₃ alkylthio,
- halogenated C₁-C₃ alkylthio,
- carbocyclic arylthio,
- carbocyclic arylthio substituted by cyano,
- C₁-C₃ alkylsulfonyl,
- mono- or di-C₁-C₃ alkylaminosulfonyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - C₁-C₇ alkyl,
 - halogenated C₁-C₇ alkyl,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
- (vi) heterocyclyl,
- or heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - oxo,
 - C₁-C₃ alkylthio,
 - C₁-C₃ alkylthio substituted by carbocyclic aryl,
 - C₁-C₃ alkylthio substituted by halogenated carbocyclic aryl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
 - heterocyclyl,

- C₁-C₃ alkoxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkylthio,
 - C₁-C₃ alkenylthio,
 - carbocyclic arylthio,
 - C₁-C₃ alkylsulfonyl,
 - carbocyclic arylsulfonyl,
 - halogenated carbocyclic arylsulfonyl,
 - carbocyclic arylsulfonyl substituted by C₁-C₄ alkyl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl;

R₂ is -NHNH₂, -NHNHBoc, -N(R_{2a})(R_{2b}), morpholino, 4-acetyl-piperazyl, or 4-phenyl-piperazyl;

wherein R_{2a} is H or C₁-C₃ alkyl;

R_{2b} is C₁-C₄ alkyl, C₁-C₄ alkyl substituted by substituent(s) independently selected from

- hydroxy,
- C₁-C₃ alkoxy,
- amino,
- NHBoc,
- C₃-C₆ cycloalkyl,
- carbocyclic aryl,

•carbocyclic aryl substituted by substituent(s) independently selected from

••halogen,

••C₁-C₃ alkyl,

••C₁-C₃ alkoxy,

••-SO₂NH₂,

•heterocyclyl,

C₃-C₆ cycloalkyl, carbocyclic aryl, carbocyclic aryl substituted by substituent(s)

independently selected from

•halogen,

•C₁-C₃ alkyl,

•C₁-C₃ alkoxy,

or a group of Formula IV;

wherein Boc is carbamic acid *tert*-butyl ester and R₃ is C₁-C₃ alkyl or C₁-C₃ alkyl substituted by substituent(s) independently selected from

•carbocyclic aryl,

•halogenated carbocyclic aryl,

•carbocyclic aryl substituted by C₁-C₃ alkoxy;

L is selected from Formula V - XIX;

wherein R₄ is H or C₁-C₃ alkyl;

R₅ is H, C₁-C₃ alkyl, or C₁-C₃ alkyl substituted by a substituted carbocyclic aryl;

Y is -C(O)-;

wherein carbocyclic aryl is phenyl, naphthyl, anthranyl, or biphenyl;

carbocyclyl is 10,11-dihydro-5-oxo-dibenzo[a,d]cycloheptyl, 1-oxo-indanyl, 9*H*-fluorenyl, 9-oxo-fluorenyl, acenaphthyl, anthraquinonyl, *C*-fluoren-9-ylidene, indanyl, indenyl, 1,2,3,4-tetrahydro-naphthyl, or bicyclo[2.2.1]hepteny;

heterocyclyl is 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,2-dihydro-3-oxo-pyrazolyl, 1,3-dioxo-isoindolyl, 1*H*-indolyl, 1*H*-pyrrolyl, 1-oxo-3*H*-isobenzofuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2,3-dihydro-benzofuryl, 2,4-dihydro-3-oxo-pyrazolyl, 2*H*-benzopyranyl, 2-oxo-benzopyranyl, 2-oxo-pyrrolidinyl, 3,4-dihydro-2*H*-benzo[b][1,4]dioxepinyl, 4-oxo-1,5,6,7-tetrahydro-indolyl, 4-oxo-3,4-dihydro-phthalazinyl, 4-oxo-benzopyranyl, 9,10,10-trioxo-thioxanthenyl, 9*H*-xanthenyl, azetidiny, benzimidazolyl, benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[b]thienyl, cinnolyl,

furyl, imidazolyl, isoxazolyl, morpholino, morpholinyl, oxazolyl, oxolanyl, piperidyl, piridyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolidyl, quinolyl, quinoxalyl, thiazolidyl, thiazolyl, thienyl, thiolanyl, tetrahydro-thienyl, benzofuranyl, or benzothiazolyl;

halogen is fluoro, chloro, bromo, or iodo.

Other preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₀ alkyl,

C₁-C₁₀ alkyl substituted by substituent(s) independently selected from

- oxo,
- di-propylaminocarbonyl,
- methoxy substituted by carbocyclic aryl,
- methylcarbonyloxy,
- carbocyclic aryloxy,
- halogenated carbocyclic aryloxy,
- carbocyclic aryloxy substituted by nitro,
- heterocyclyloxy substituted by methyl,
- substituted heterocyclyl-ethylideneaminoxy,
- tert*-butoxycarbonylamino,
- carbocyclic arylcarbonylamino,
- C₁-C₂ alkylthio,
- C₁-C₂ alkylthio substituted by substituent(s) independently selected from
 - halogenated carbocyclic aryl,
 - carbocyclic aryl substituted by methoxy,
- carbocyclic arylthio,
- heterocyclylthio substituted by nitro,
- heterocyclylthio substituted by methyl,
- C₅-C₆ cycloalkyl,
- C₅-C₆ cycloalkenyl,
- carbocyclyl substituted by substituent(s) independently selected from

- halogen,
 - methyl,
 - methoxy,
 - ethenyl substituted by carbocyclic aryl substituted methylsulfinyl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - oxo,
 - carbocyclic aryl,
 - heterocyclyl,
 - C₁-C₄ alkoxy,
 - halogenated C₁-C₄ alkoxy,
 - C₁-C₄ alkoxy substituted by carbocyclic aryl,
 - carbocyclic aryloxy,
 - halogenated mono-carbocyclic arylaminocarbonyl,
 - carbocyclic aryl,
 - heterocyclyl,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₂ alkyl,
 - C₁-C₂ substituted by carbocyclic aryl,
 - methoxy,
 - methoxy substituted by carbocyclic aryl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
- (ii) C₂-C₃ alkenyl substituted by substituent(s) independently selected from
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,

- carbocyclic aryl substituted by nitro,
- (iii) C₃-C₆ cycloalkyl,
C₃-C₆ cycloalkyl substituted by substituent(s) independently selected from
 - methyl substituted by oxo,
 - methyl substituted by carbocyclic aryl,
 - carbocyclic aryl,
- (iv) carbocyclyl,
(v) carbocyclic aryl,
carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - nitro,
 - C₁-C₉ alkyl,
 - C₁-C₉ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - oxo,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by methyl,
 - carbocyclic aryloxy,
 - C₁-C₇ alkoxy,
 - halogenated C₁-C₇ alkoxy,
 - C₁-C₇ alkoxy substituted by carbocyclic aryl,
 - methylcarbonyloxy,
 - carbocyclic aryloxy,
 - carbocyclic aryloxy substituted by methoxy,
 - amino,
 - di-methylamino,
 - propargynylcarbonylamino substituted by carbocyclic aryl,
 - carbocyclic arylsulfonylamino substituted by methyl,
 - (carbocyclic aryl)NHC(O)NH substituted by halogenated methoxy,
 - halogenated methylthio,

- carbocyclic arylthio substituted by cyano,
- di-propylamino sulfonyl,
- mono- or di- ethylaminocarbonyl substituted by carbocyclic aryl,
- carbocyclic aryl,
- heterocyclyl substituted by methyl,
- heterocyclyl substituted by halogenated carbocyclic aryl,
- (vi) heterocyclyl,
- or heterocyclyl substituted by substituent(s) independently selected from
- halogen,
- nitro,
- C₁-C₄ alkyl,
- C₁-C₄ alkyl substituted by substituent(s) independently selected from
- halogen,
- methylthio substituted by halogenated carbocyclic aryl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- heterocyclyl,
- methoxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by methyl,
- C₁-C₃ alkylthio,
- propenylthio,
- carbocyclic arylthio,
- C₁-C₃ alkylsulfonyl,
- carbocyclic arylsulfonyl substituted by C₁-C₄ alkyl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by methyl,
- carbocyclic aryl substituted by nitro,
- heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula Va, VIIIa, or IXa;

wherein R₄ and R₅ are independently selected from H or C₁-C₃ alkyl;

Y is -C(O)-;

wherein carbocyclic aryl is phenyl, naphthyl, anthranyl, or biphenyl;

carbocyclyl is 1-oxo-indanyl, 9-oxo-fluorenyl, indenyl, anthraquinonyl, C-fluoren-9-ylidene, 1,2,3,4-tetrahydro-naphthyl, or bicyclo[2.2.1]hepteny;

heterocyclyl is 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,2-dihydro-3-oxo-pyrazolyl, 1,3-dioxo-isoindolyl, 1*H*-indolyl, 1*H*-pyrrolyl, 1-oxo-3*H*-isobenzofuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2,4-dihydro-3-oxo-pyrazolyl, 2*H*-benzopyranyl, 2-oxo-benzopyranyl, 3,4-dihydro-2*H*-benzo[b][1,4]dioxepinyl, 4-oxo-3,4-dihydro-phthalazinyl, 4-oxo-benzopyranyl, 9,10,10-trioxo-thioxanthenyl, 9*H*-xanthenyl, azetidiny, benzimidazolyl, benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[b]thienyl, furyl, imidazolyl, isoxazolyl, morpholino, morpholinyl, oxolanyl, piperidyl, piridyl, pyrazolyl, pyridyl, quinolyl, quinoxalyl, thiazolidyl, thiazolyl, thienyl, thiolanyl, 2,3-dihydro-1-oxo-isoindolyl, 2,3-dihydro-benzofuryl, 2-oxo-pyrrolidinyl, 4-oxo-1,5,6,7-tetrahydro-indolyl, cinnolyl, pyrimidyl, pyrrolidyl, tetrahydro-thienyl, benzofuranyl, or benzothiazolyl;

halogen is fluoro, chloro, bromo, or iodo.

Other more preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₀ alkyl substituted by substituent(s) independently selected from

- oxo,
- di-propylaminocarbonyl,
- methoxy substituted by carbocyclic aryl,
- methylcarbonyloxy,
- carbocyclic aryloxy,
- halogenated carbocyclic aryloxy,
- carbocyclic aryloxy substituted by nitro,
- heterocyclyloxy substituted by methyl,
- substituted heterocyclyl-ethylideneaminooxy,
- tert*-butoxycarbonylamino,

- carbocyclic arylcarbonylamino,
- C₁-C₂ alkylthio,
- C₁-C₂ alkylthio substituted by substituent(s) independently selected from
 - halogenated carbocyclic aryl,
 - carbocyclic aryl substituted by methoxy,
- carbocyclic arylthio,
- heterocyclylthio substituted by nitro,
- heterocyclylthio substituted by methyl,
- C₅-C₆ cycloalkenyl,
- carbocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - methyl,
 - methoxy,
 - ethenyl substituted by carbocyclic aryl substituted methylsulfinyl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - oxo,
 - carbocyclic aryl,
 - heterocyclyl,
 - C₁-C₄ alkoxy,
 - halogenated C₁-C₄ alkoxy,
 - C₁-C₄ alkoxy substituted by carbocyclic aryl,
 - carbocyclic aryloxy,
 - halogenated mono-carbocyclic arylaminocarbonyl,
- carbocyclic aryl,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₂ alkyl,

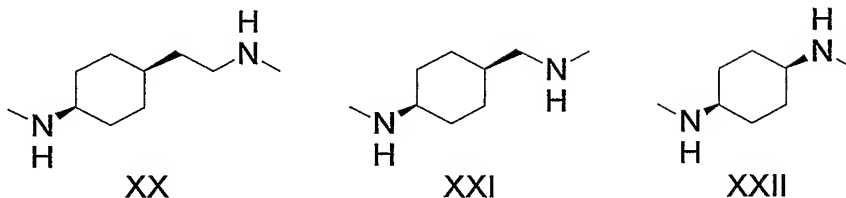
- C₁-C₂ substituted by carbocyclic aryl,
- methoxy,
- methoxy substituted by carbocyclic aryl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- (ii) C₂-C₃ alkenyl substituted by substituent(s) independently selected from
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
 - carbocyclic aryl substituted by nitro,
- (iii) C₃-C₆ cycloalkyl substituted by substituent(s) independently selected from
 - methyl substituted by oxo,
 - methyl substituted by carbocyclic aryl,
 - carbocyclic aryl,
- (iv) carbocyclyl,
- (v) carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - nitro,
 - C₁-C₉ alkyl,
 - C₁-C₉ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - oxo,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by methyl,
 - carbocyclic aryloxy,
 - C₁-C₇ alkoxy,
 - halogenated C₁-C₇ alkoxy,
 - C₁-C₇ alkoxy substituted by carbocyclic aryl,
 - methylcarbonyloxy,
 - carbocyclic aryloxy,
 - carbocyclic aryloxy substituted by methoxy,

- amino,
- di-methylamino,
- propargynylcarbonylamino substituted by carbocyclic aryl,
- carbocyclic arylsulfonylamino substituted by methyl,
- (carbocyclic aryl)NHC(O)NH substituted by halogenated methoxy,
- halogenated methylthio,
- carbocyclic arylthio substituted by cyano,
- di-propylamino sulfonyl,
- mono- or di- ethylaminocarbonyl substituted by carbocyclic aryl,
- carbocyclic aryl,
- heterocyclyl substituted by methyl,
- heterocyclyl substituted by halogenated carbocyclic aryl,
- (vi) or heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - methylthio substituted by halogenated carbocyclic aryl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
 - heterocyclyl,
 - methoxy,
 - carbocyclic aryloxy,
 - carbocyclic aryloxy substituted by methyl,
 - C₁-C₃ alkylthio,
 - propenylthio,
 - carbocyclic arylthio,
 - C₁-C₃ alkylsulfonyl,
 - carbocyclic arylsulfonyl,
 - carbocyclic arylsulfonyl substituted by C₁-C₄ alkyl,
 - carbocyclic aryl,

- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by methyl,
- carbocyclic aryl substituted by nitro,
- heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula XX - XXII;



Y is -C(O)-;

wherein carbocyclic aryl is phenyl, naphthyl, or biphenyl;

carbocyclyl is 1-oxo-indanyl, 9-oxo-fluorenyl, indenyl, anthraquinonyl, C-fluoren-9-ylidene, 1,2,3,4-tetrahydro-naphthyl, or bicyclo[2.2.1]hepteny;

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halogen is fluoro, chloro, bromo, or iodo.

Further other more preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₅ alkyl substituted by substituent(s) independently selected from

- oxo,
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- methoxy substituted by carbocyclic aryl,
- methylcarbonyloxy,
- carbocyclic aryloxy,
- halogenated carbocyclic aryloxy,
- carbocyclic aryloxy substituted by nitro,
- heterocyclyloxy substituted by methyl,
- substituted heterocyclyl-ethylideneaminoxy,
- tert*-butoxycarbonylamino,
- carbocyclic arylcarbonylamino,
- C₁-C₂ alkylthio,
- C₁-C₂ alkylthio substituted by substituent(s) independently selected from
 - halogenated carbocyclic aryl,
 - carbocyclic aryl substituted by methoxy,
 - carbocyclic arylthio,
 - heterocyclylthio substituted by nitro,
 - heterocyclylthio substituted by methyl,
 - cyclohexenyl,
 - carbocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - methyl,
 - methoxy,
 - ethenyl substituted by carbocyclic aryl substituted methylsulfinyl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - oxo,
 - carbocyclic aryl,
 - heterocyclyl,
 - C₁-C₂ alkoxy,

- halogenated C₁-C₂ alkoxy,
- C₁-C₂ alkoxy substituted by carbocyclic aryl,
- carbocyclic aryloxy,
- halogenated mono-carbocyclic arylaminocarbonyl,
- carbocyclic aryl,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₂ alkyl,
 - C₁-C₂ substituted by carbocyclic aryl,
 - methoxy,
 - methoxy substituted by carbocyclic aryl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
- (ii) C₂-C₃ alkenyl substituted by substituent(s) independently selected from
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
 - carbocyclic aryl substituted by nitro,
- (iii) C₃-C₆ cycloalkyl substituted by substituent(s) independently selected from
 - methyl substituted by oxo,
 - methyl substituted by carbocyclic aryl,
 - carbocyclic aryl,
- (iv) carbocyclyl,
- (v) carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₂ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - oxo,
 - carbocyclic aryl,

- carbocyclic aryl substituted by methyl,
- carbocyclic aryloxy,
- C₁-C₂ alkoxy,
- halogenated C₁-C₂ alkoxy,
- C₁-C₂ alkoxy substituted by carbocyclic aryl,
- methylcarbonyloxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by methoxy,
- amino,
- di-methylamino,
- propargynylcarbonylamino substituted by carbocyclic aryl,
- carbocyclic arylsulfonylamino substituted by methyl,
- (carbocyclic aryl)NHC(O)NH substituted by halogenated methoxy,
- halogenated methylthio,
- carbocyclic arylthio substituted by cyano,
- di-propylamino sulfonyl,
- mono- or di- ethylaminocarbonyl substituted by carbocyclic aryl,
- carbocyclic aryl,
- heterocyclyl substituted by methyl,
- heterocyclyl substituted by halogenated carbocyclic aryl,
- (vi) or heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - methylthio substituted by halogenated carbocyclic aryl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
 - heterocyclyl,
 - methoxy,
 - carbocyclic aryloxy,

- carbocyclic aryloxy substituted by methyl,
- C₁-C₃ alkylthio,
- propenylthio,
- carbocyclic arylthio,
- C₁-C₃ alkylsulfonyl,
- carbocyclic arylsulfonyl,
- carbocyclic arylsulfonyl substituted by methyl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by methyl,
- carbocyclic aryl substituted by nitro,
- heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula XX - XXII;

Y is -C(O)-;

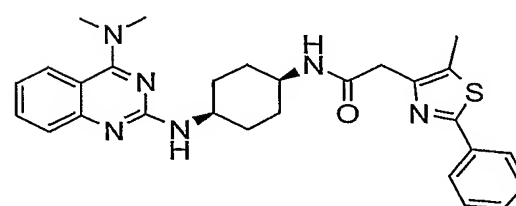
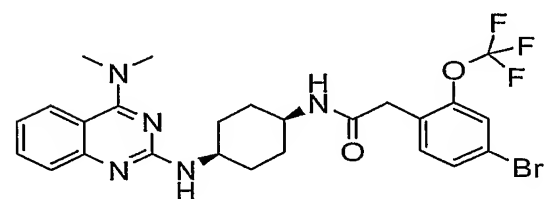
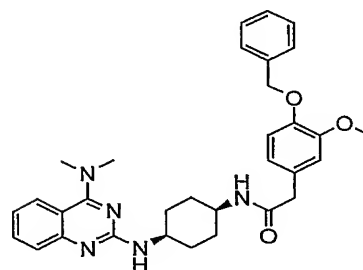
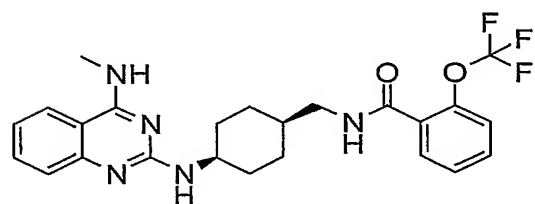
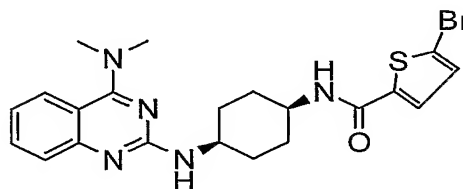
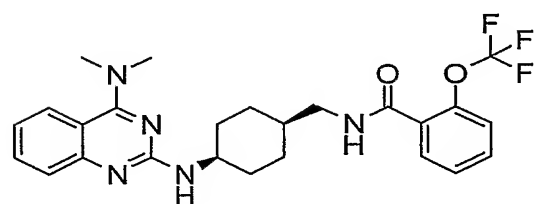
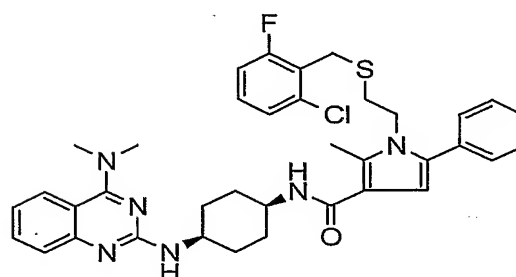
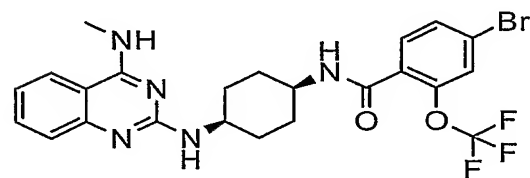
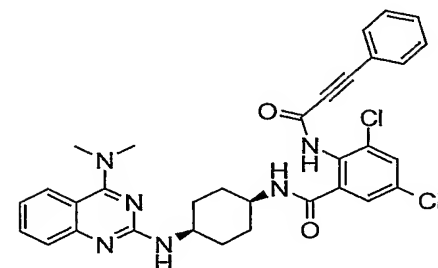
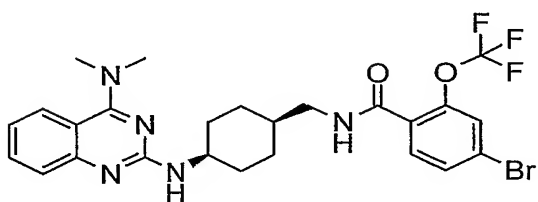
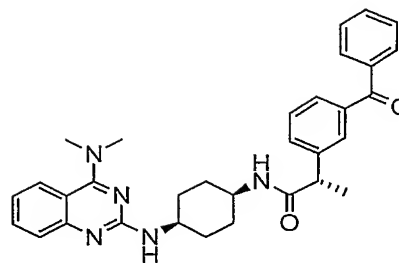
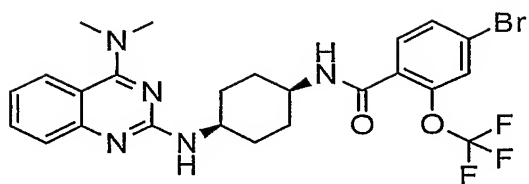
wherein carbocyclic aryl is phenyl, naphthyl, or biphenyl;

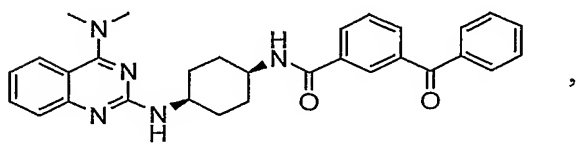
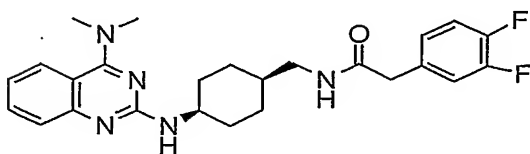
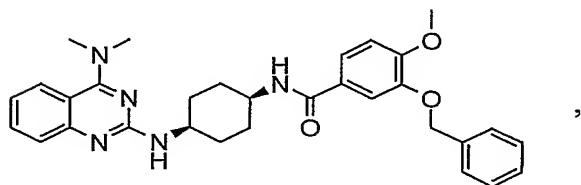
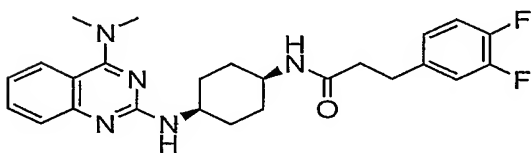
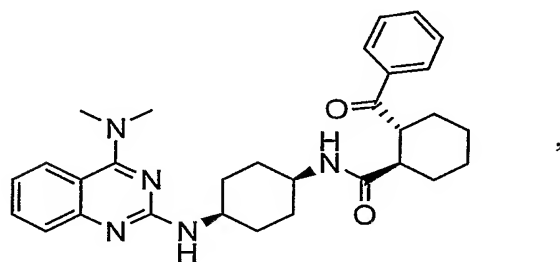
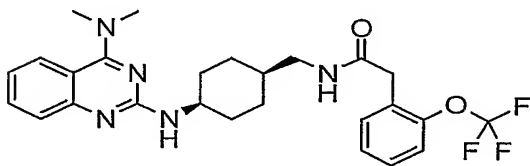
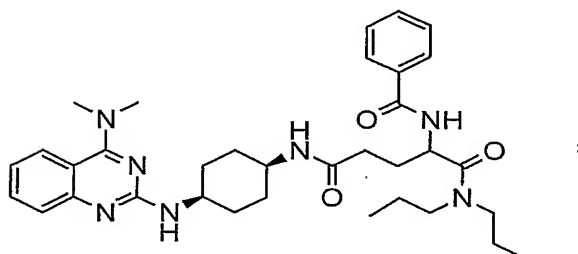
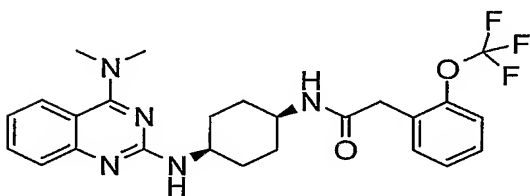
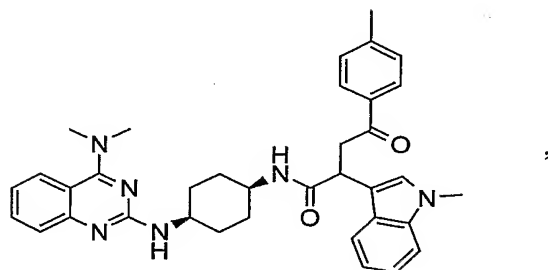
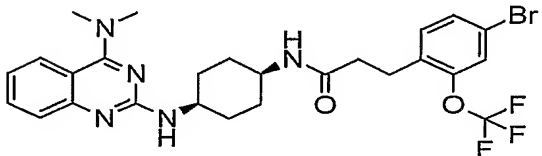
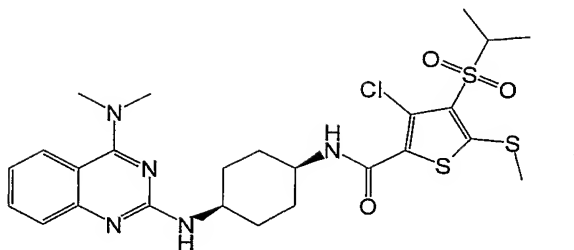
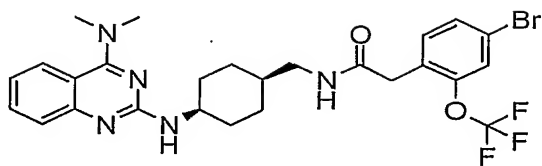
carbocyclyl is 1-oxo-indanyl, indenyl, 9-oxo-fluorenyl, 1,2,3,4-tetrahydro-naphthyl, or bicyclo[2.2.1]hepteny;

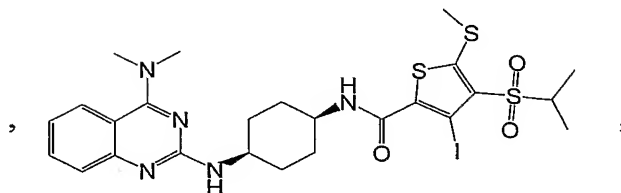
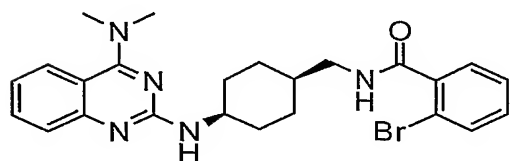
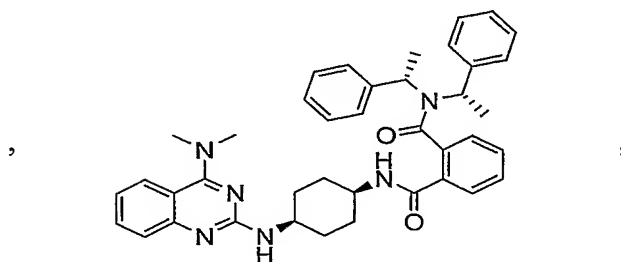
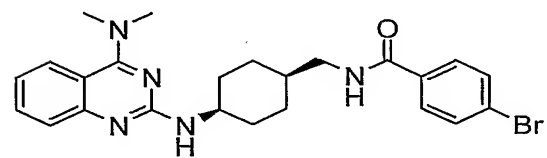
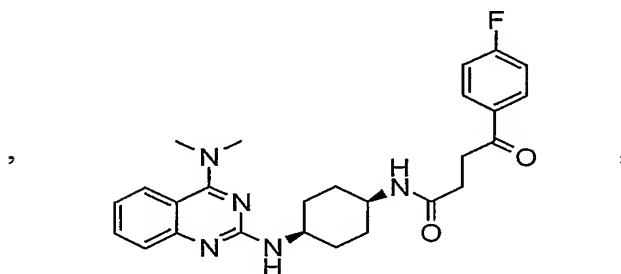
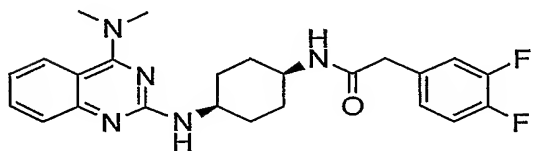
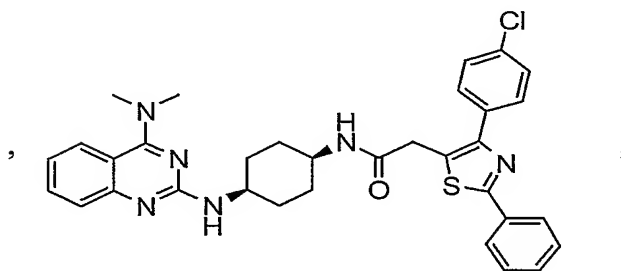
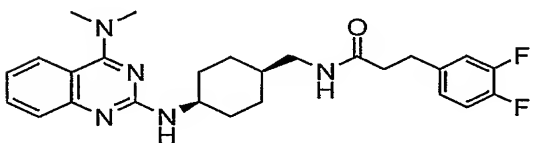
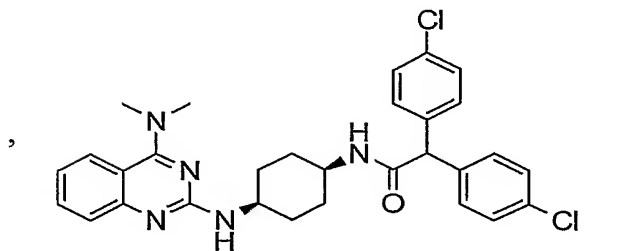
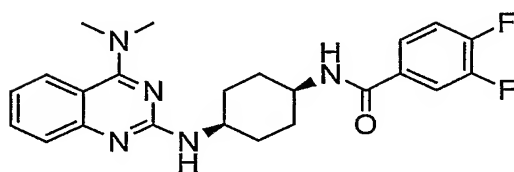
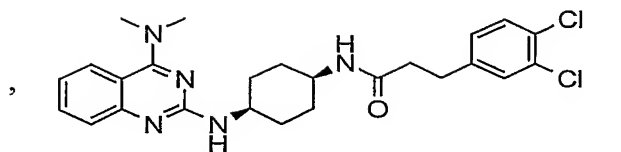
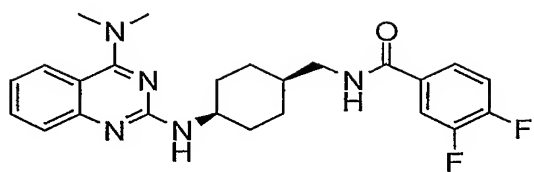
heterocyclyl is 1*H*-indolyl, 2,4-dihydro-3-oxo-pyrazolyl, furyl, pyrazolyl, pyridyl, thienyl, 1,2,3-triazolyl, 1*H*-pyrrolyl, 2,3-dihydro-1-oxo-isoindolyl, 2,3-dihydro-benzofuryl, 2*H*-benzopyranyl, 2-oxo-benzopyranyl, 4-oxo-1,5,6,7-tetrahydro-indolyl, imidazolyl, isoxazolyl, morpholino, morpholinyl, pyrazolyl, pyrimidyl, quinolyl, thiazolyl, tetrahydro-thienyl, benzofuranyl, or benzothiazolyl;

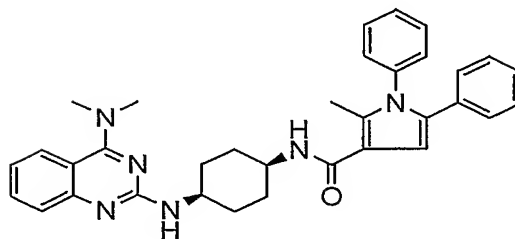
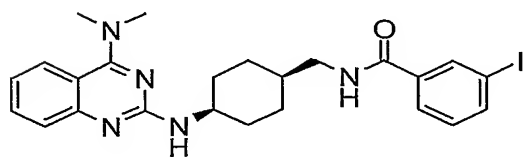
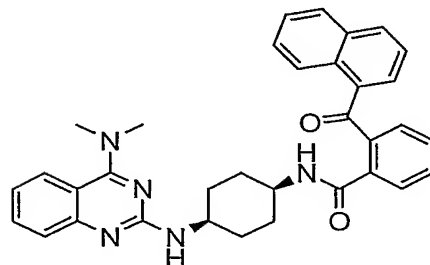
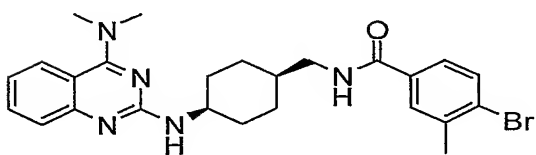
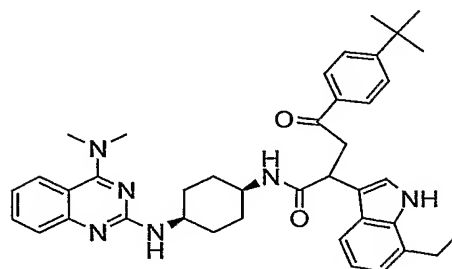
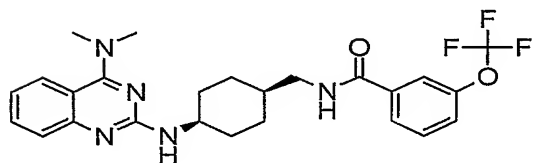
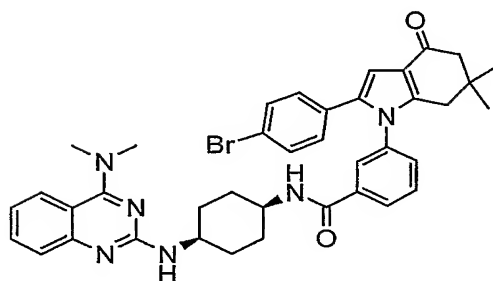
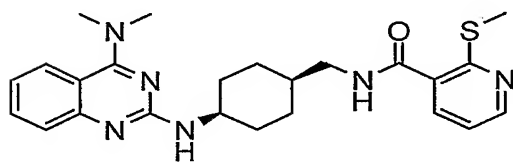
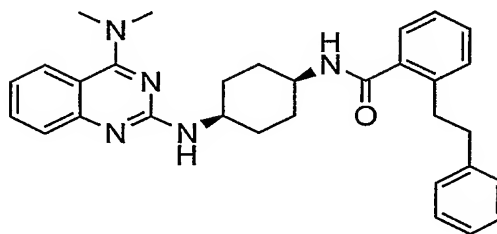
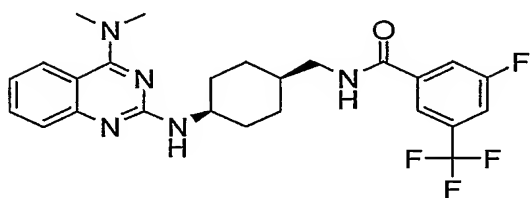
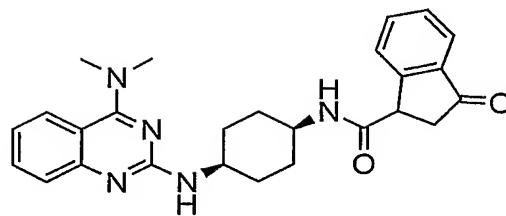
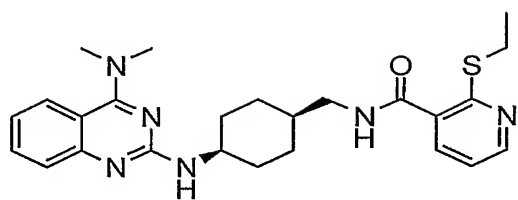
halogen is fluoro, chloro, bromo, or iodo.

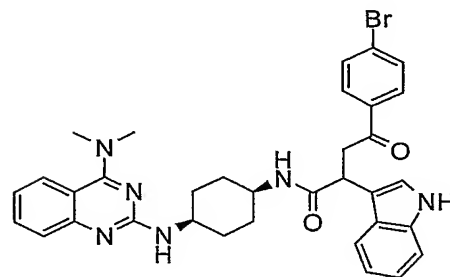
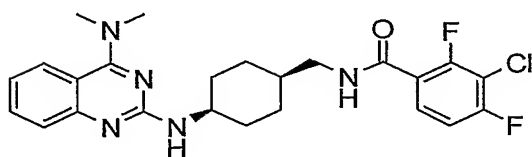
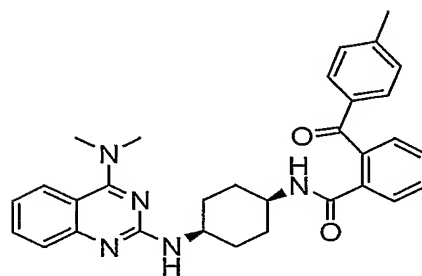
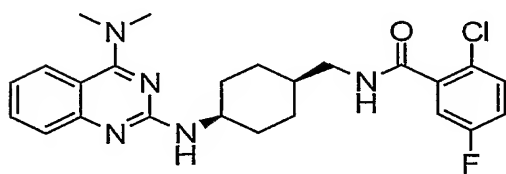
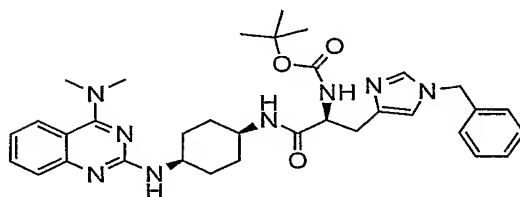
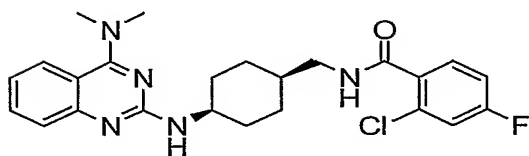
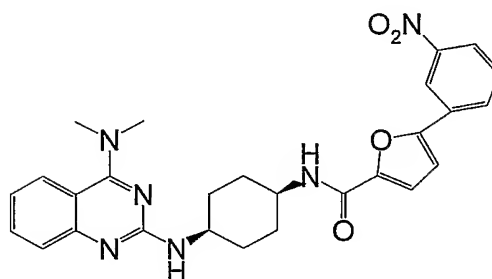
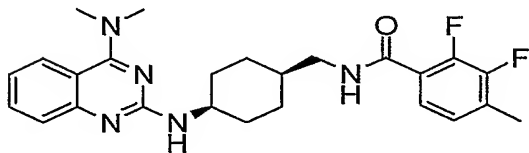
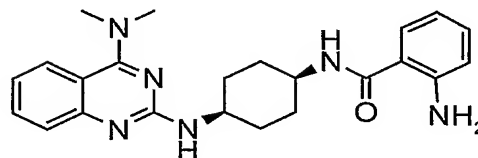
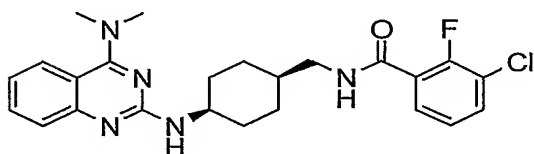
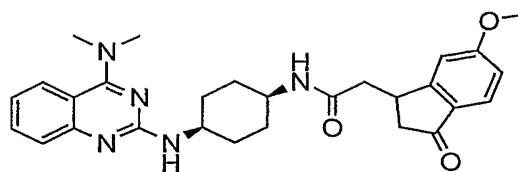
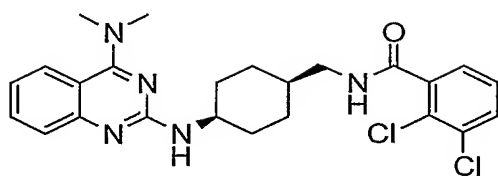
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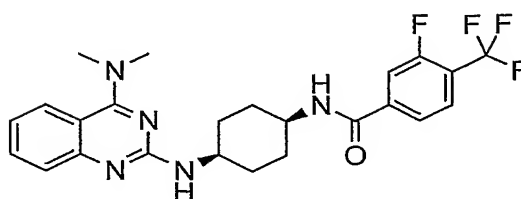
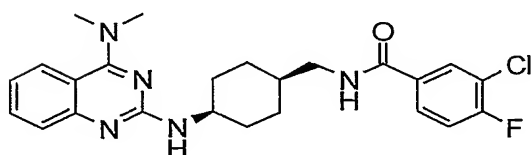
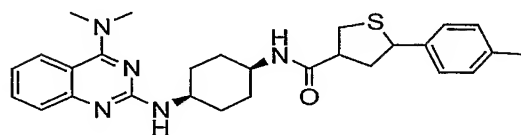
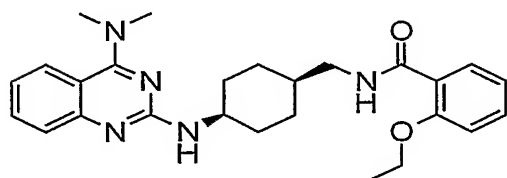
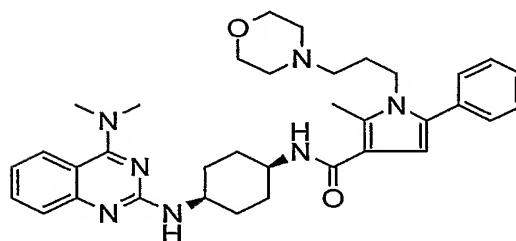
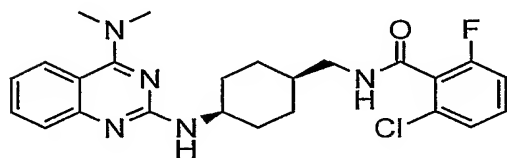
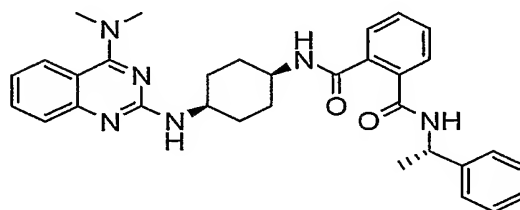
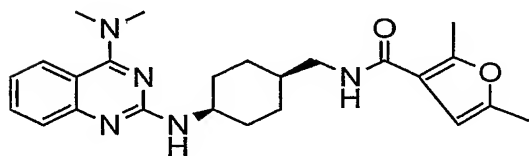
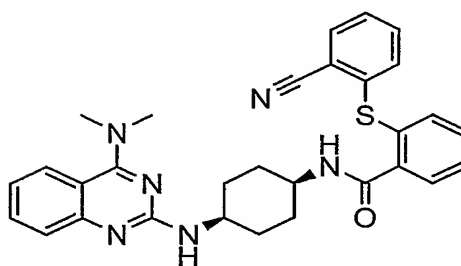
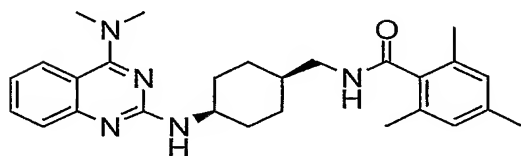
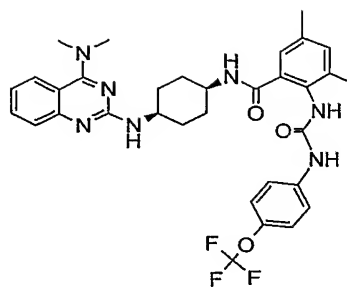
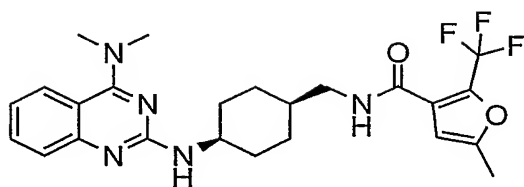


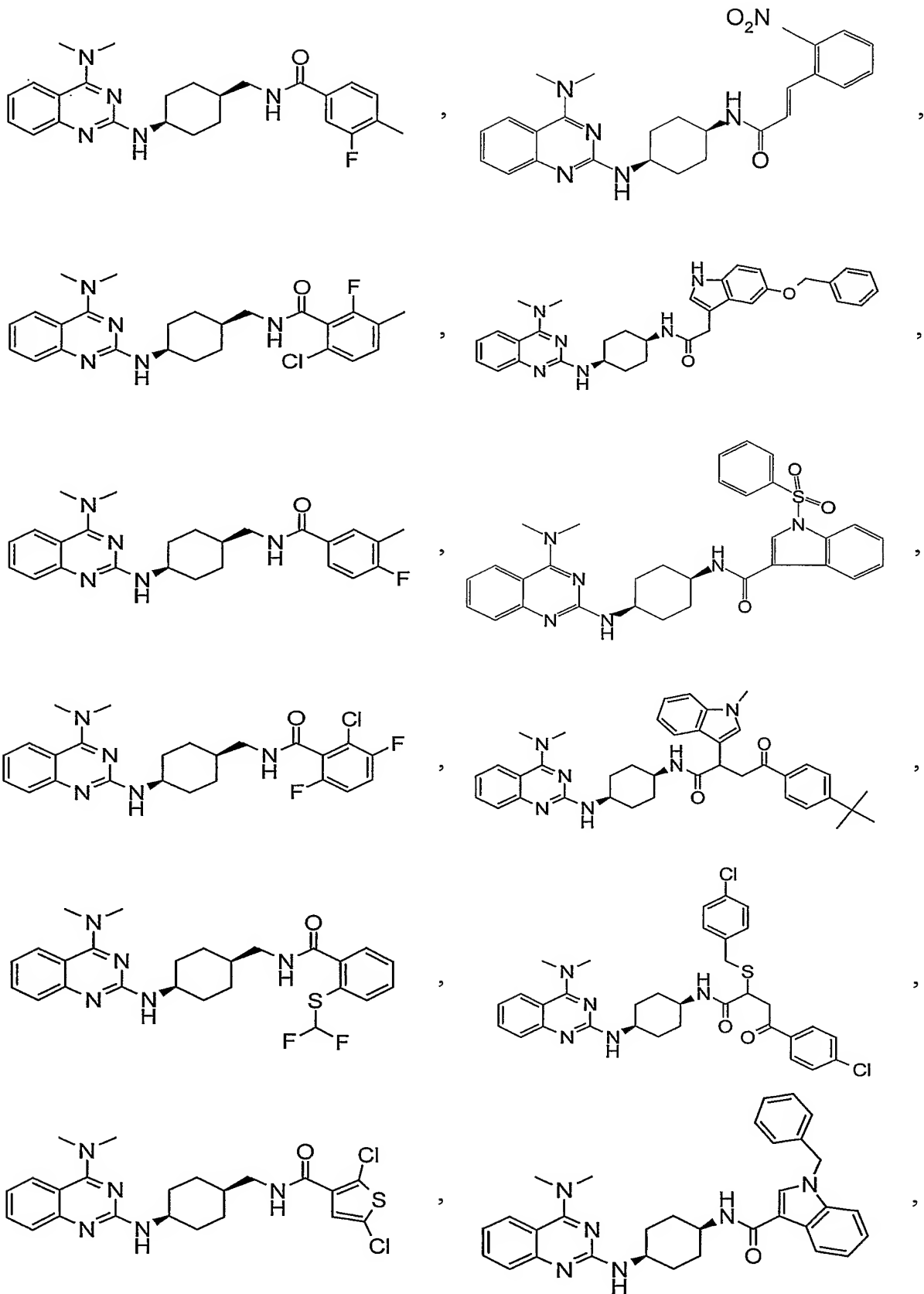


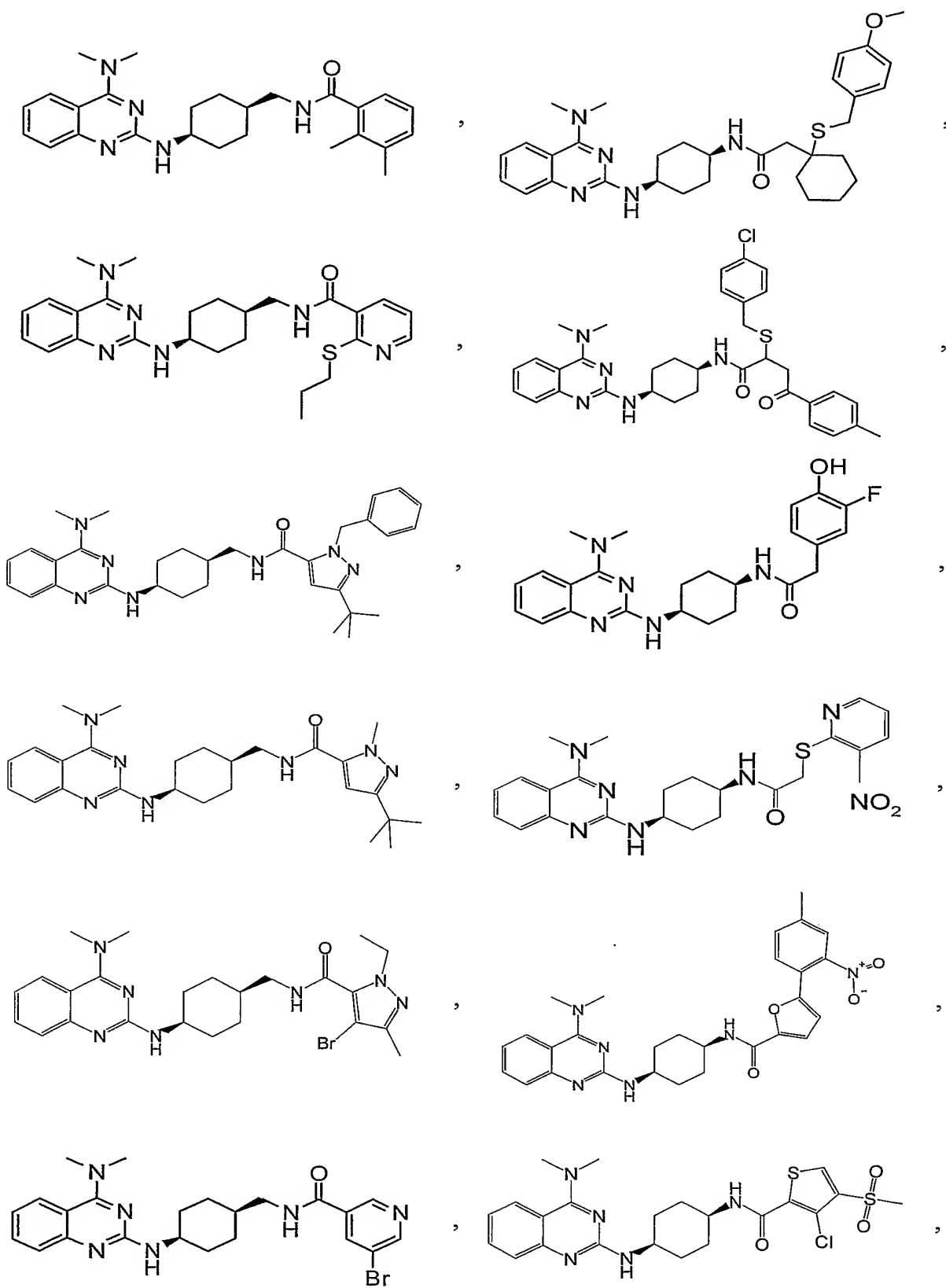


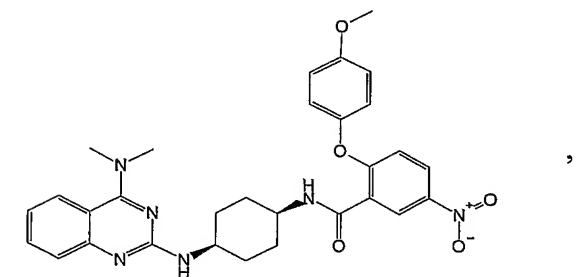
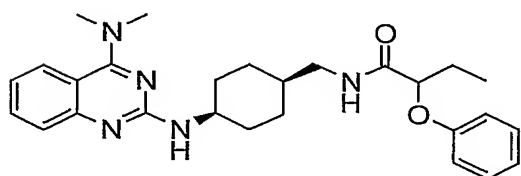
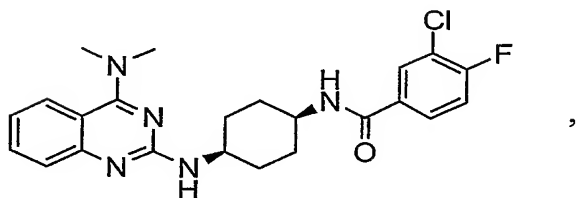
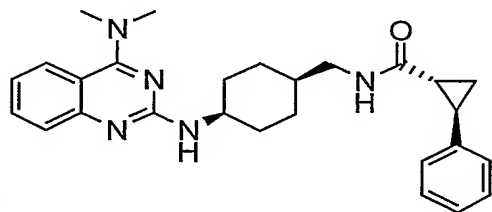
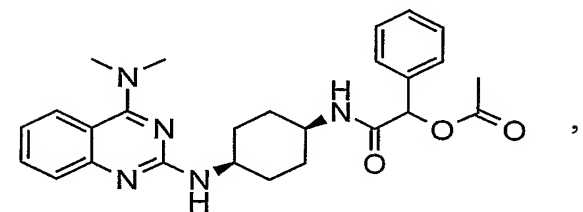
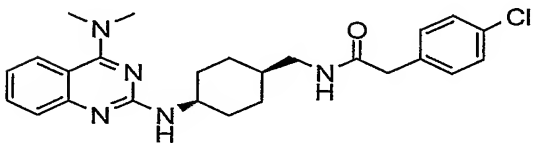
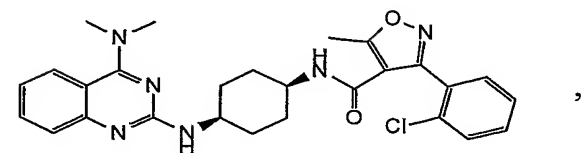
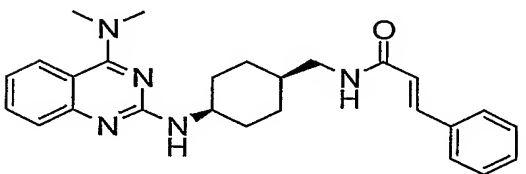
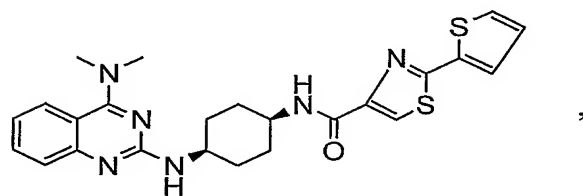
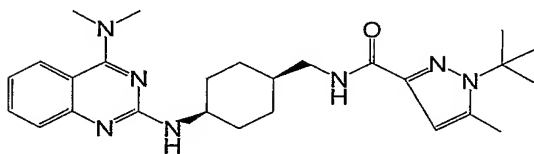
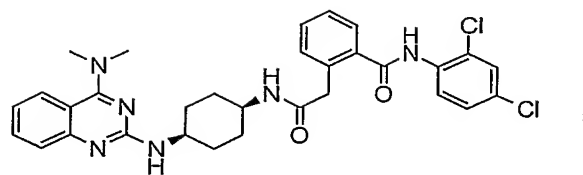
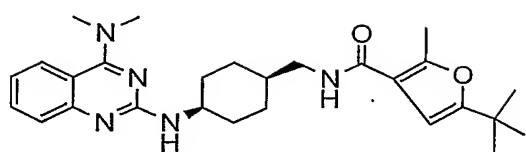


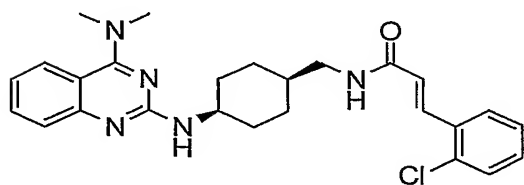
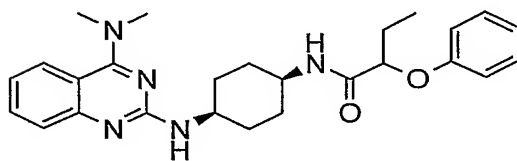
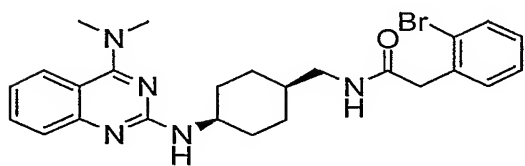
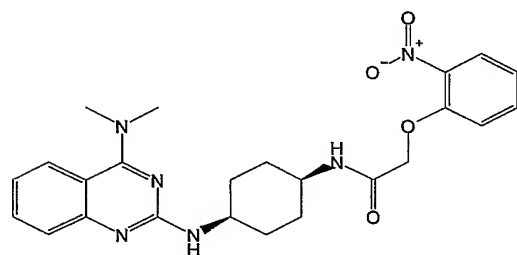
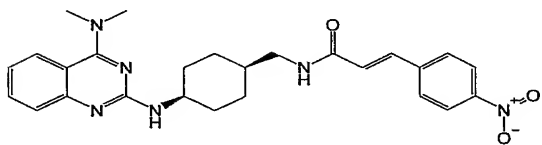
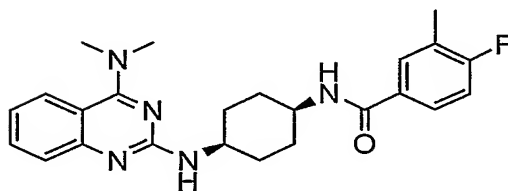
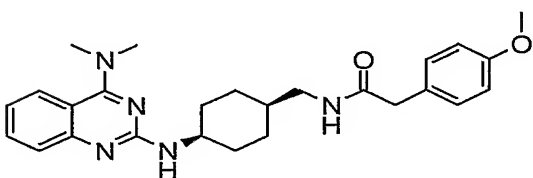
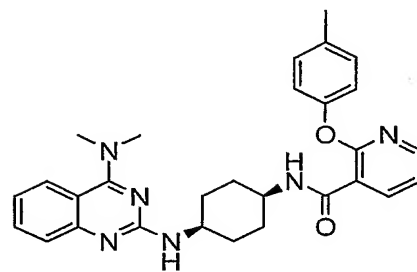
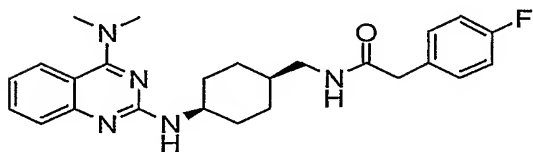
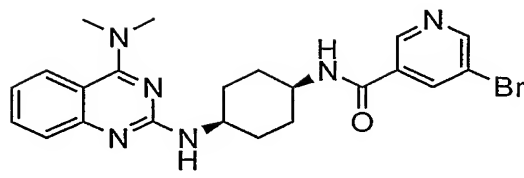
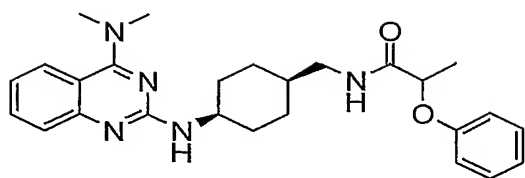


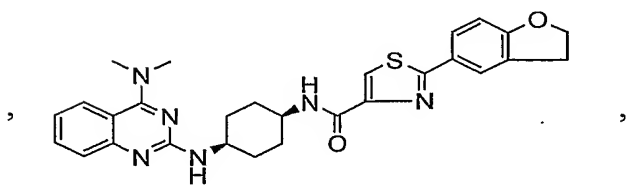
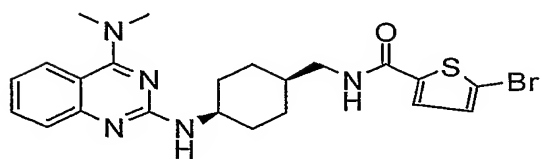
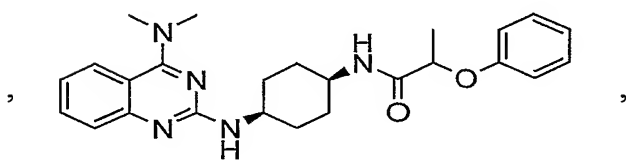
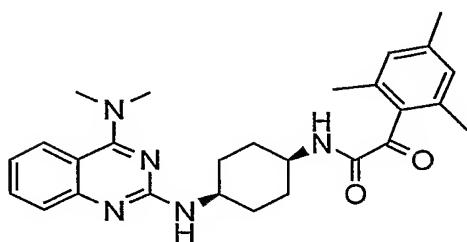
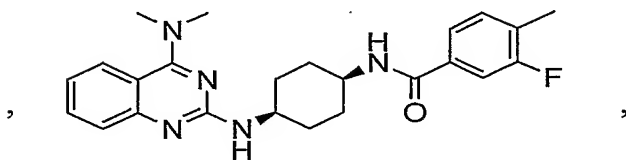
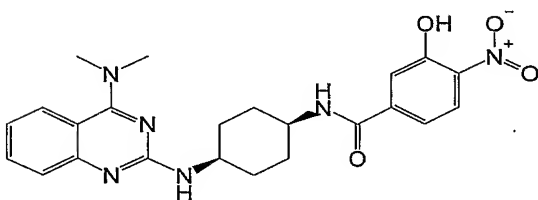
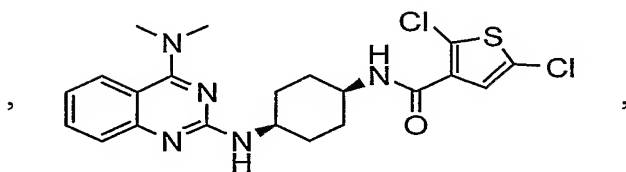
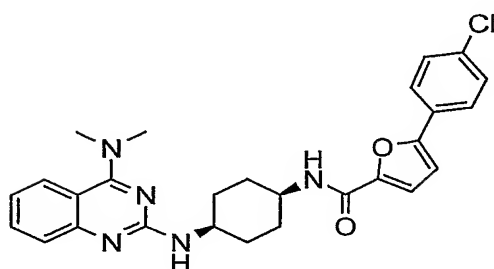
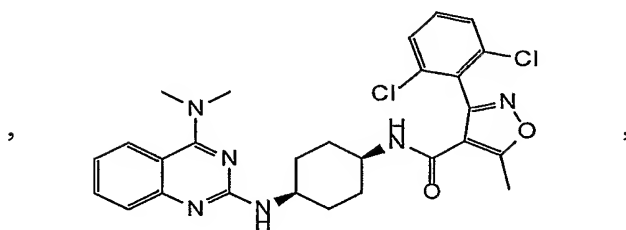
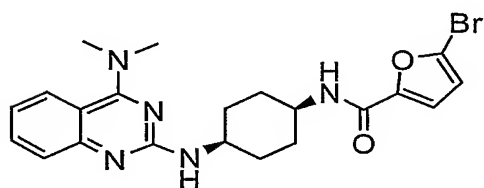
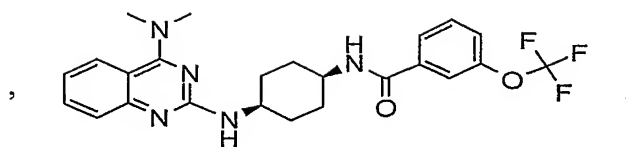
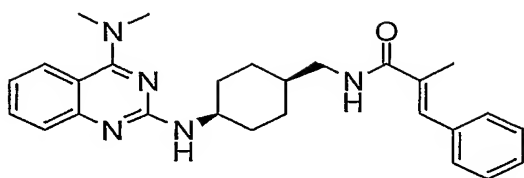


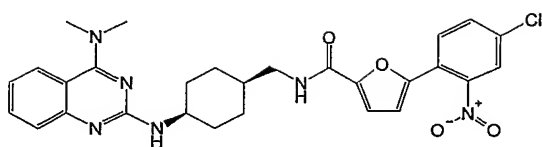




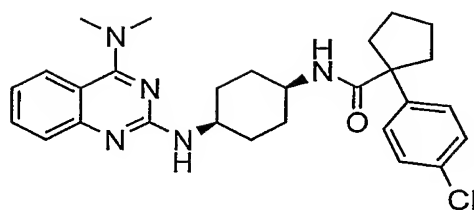




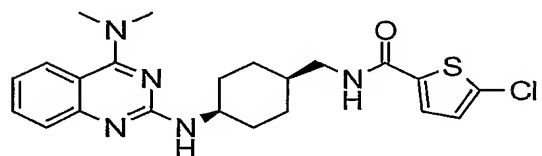




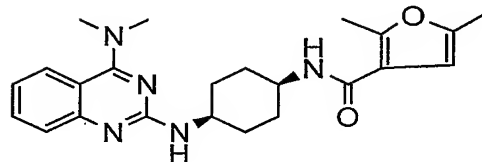
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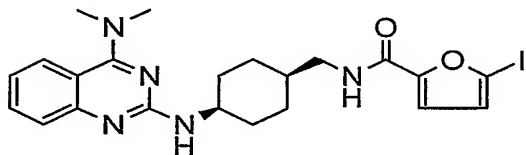
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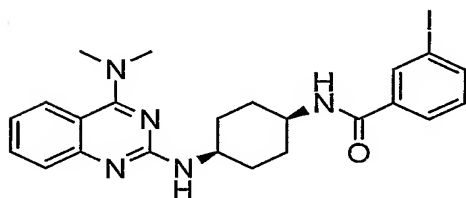
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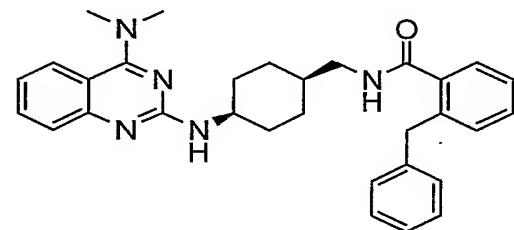
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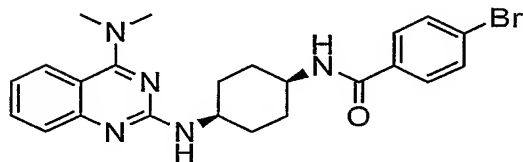
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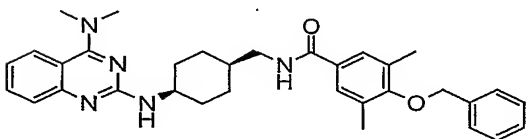
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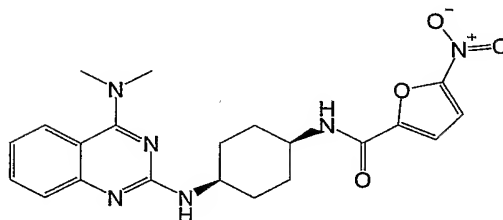
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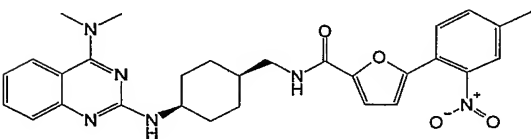
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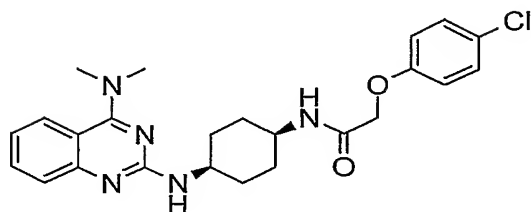
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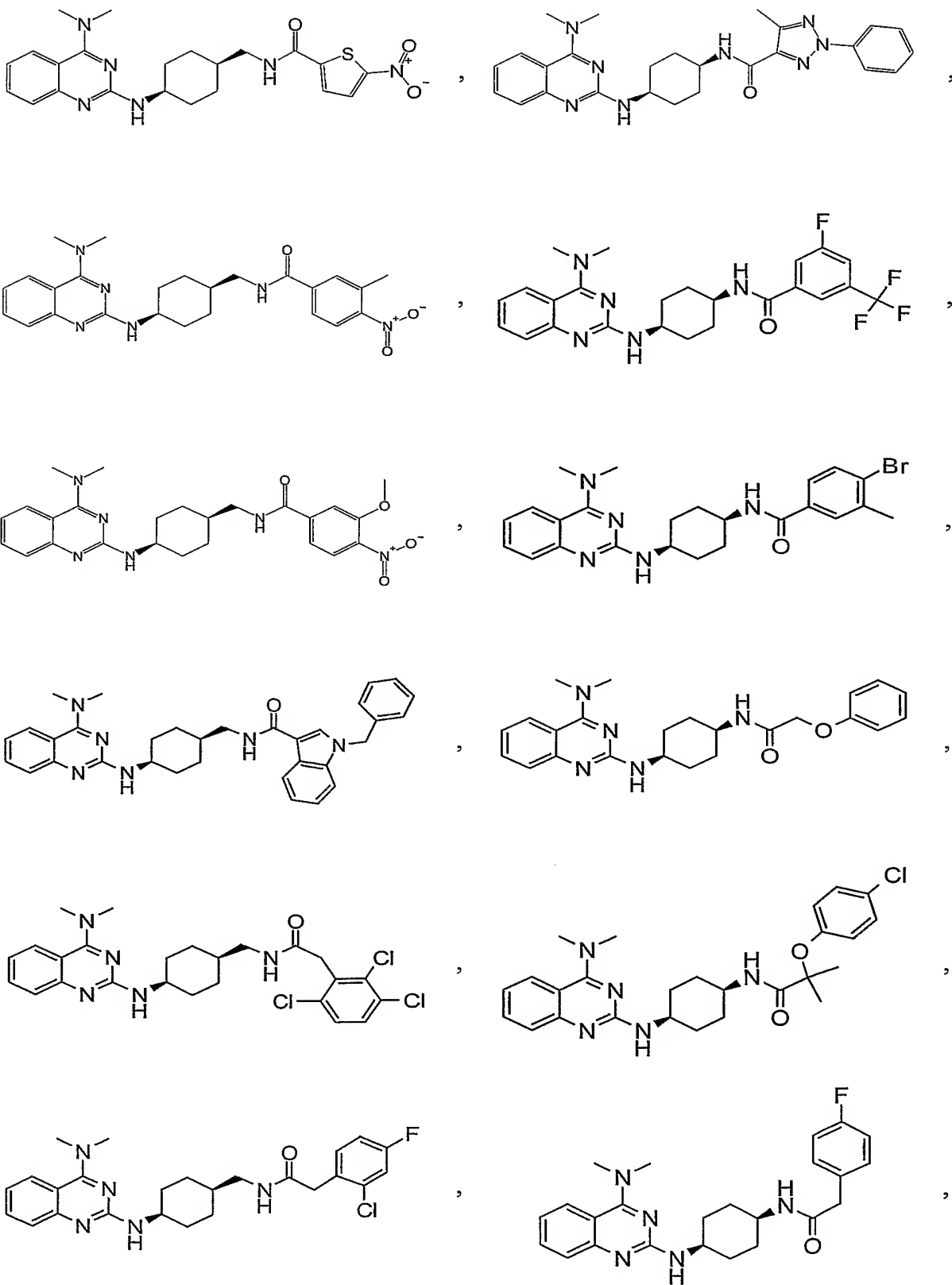
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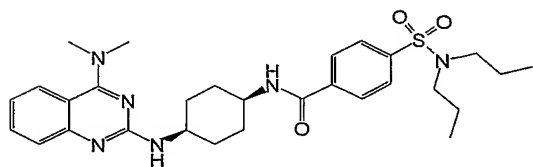
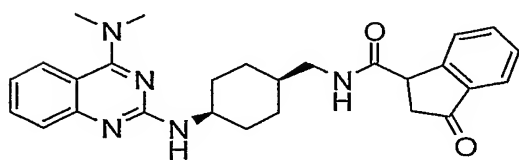
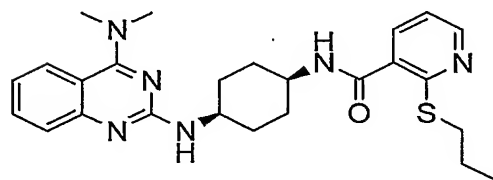
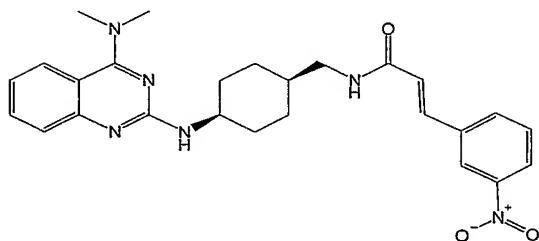
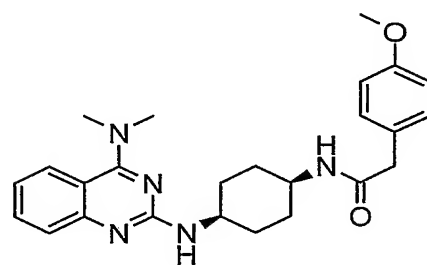
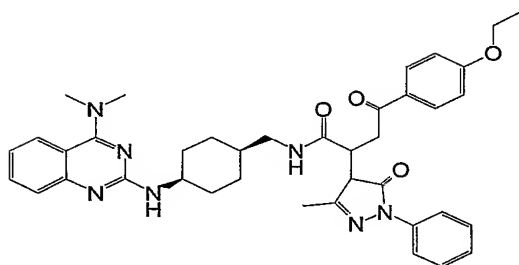
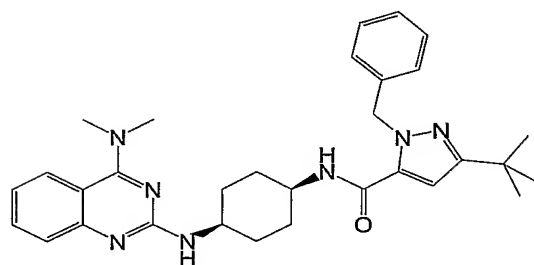
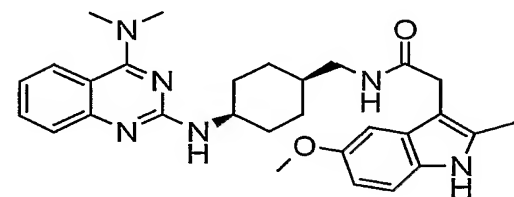
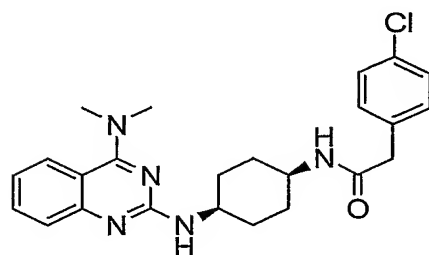
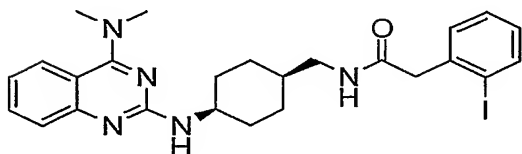
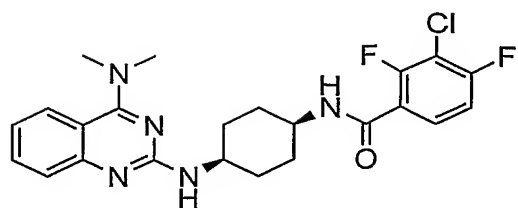
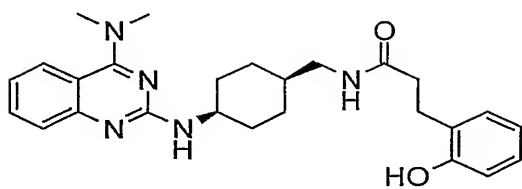


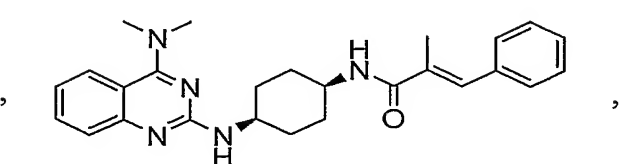
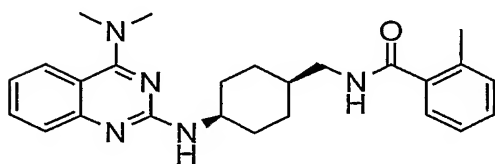
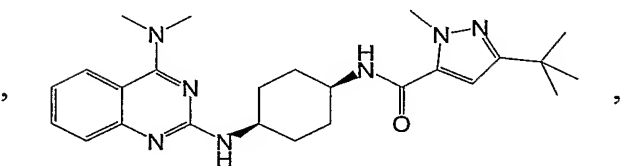
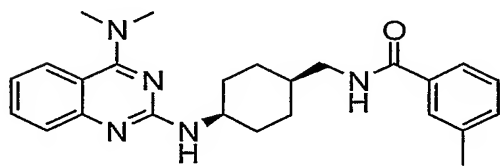
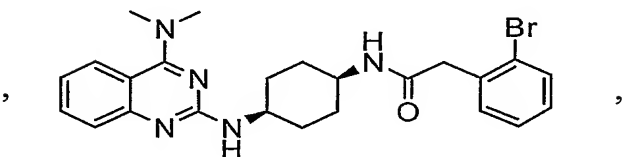
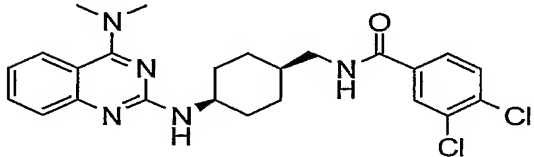
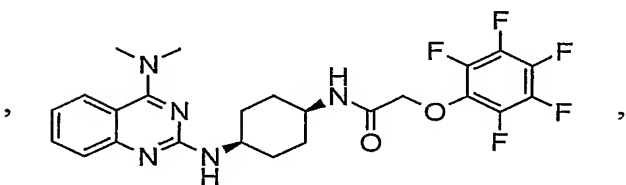
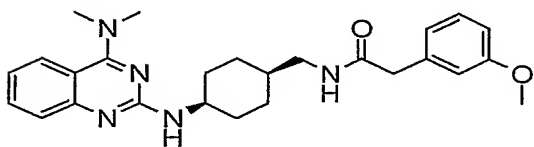
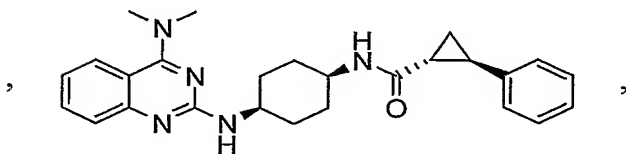
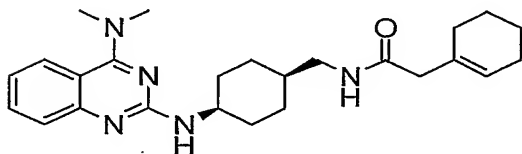
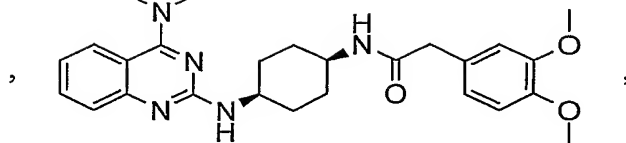
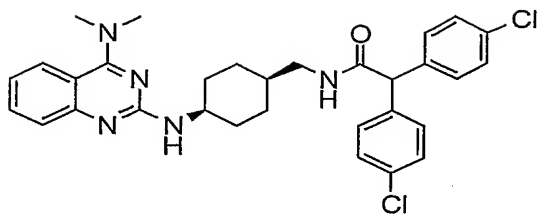
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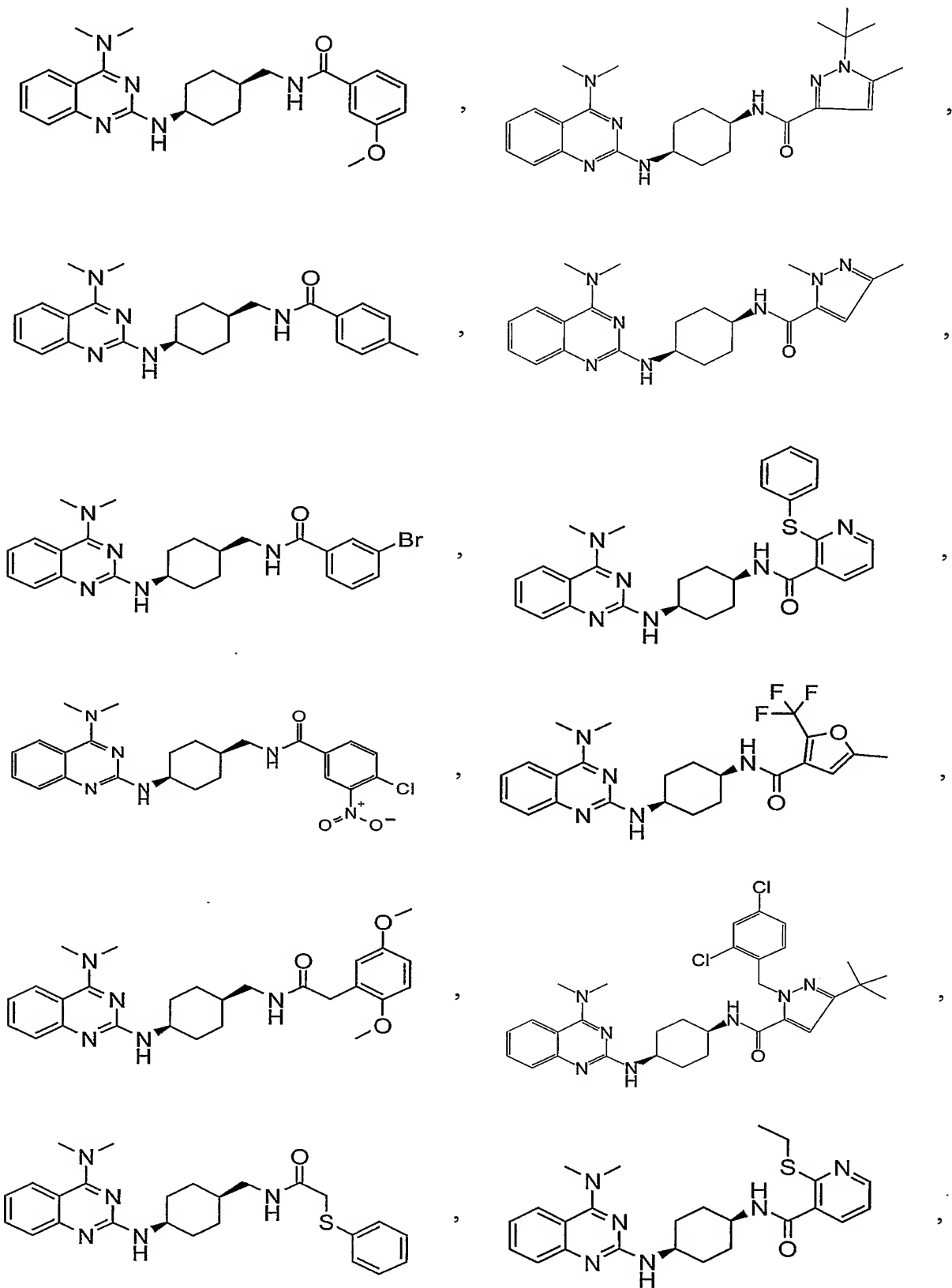


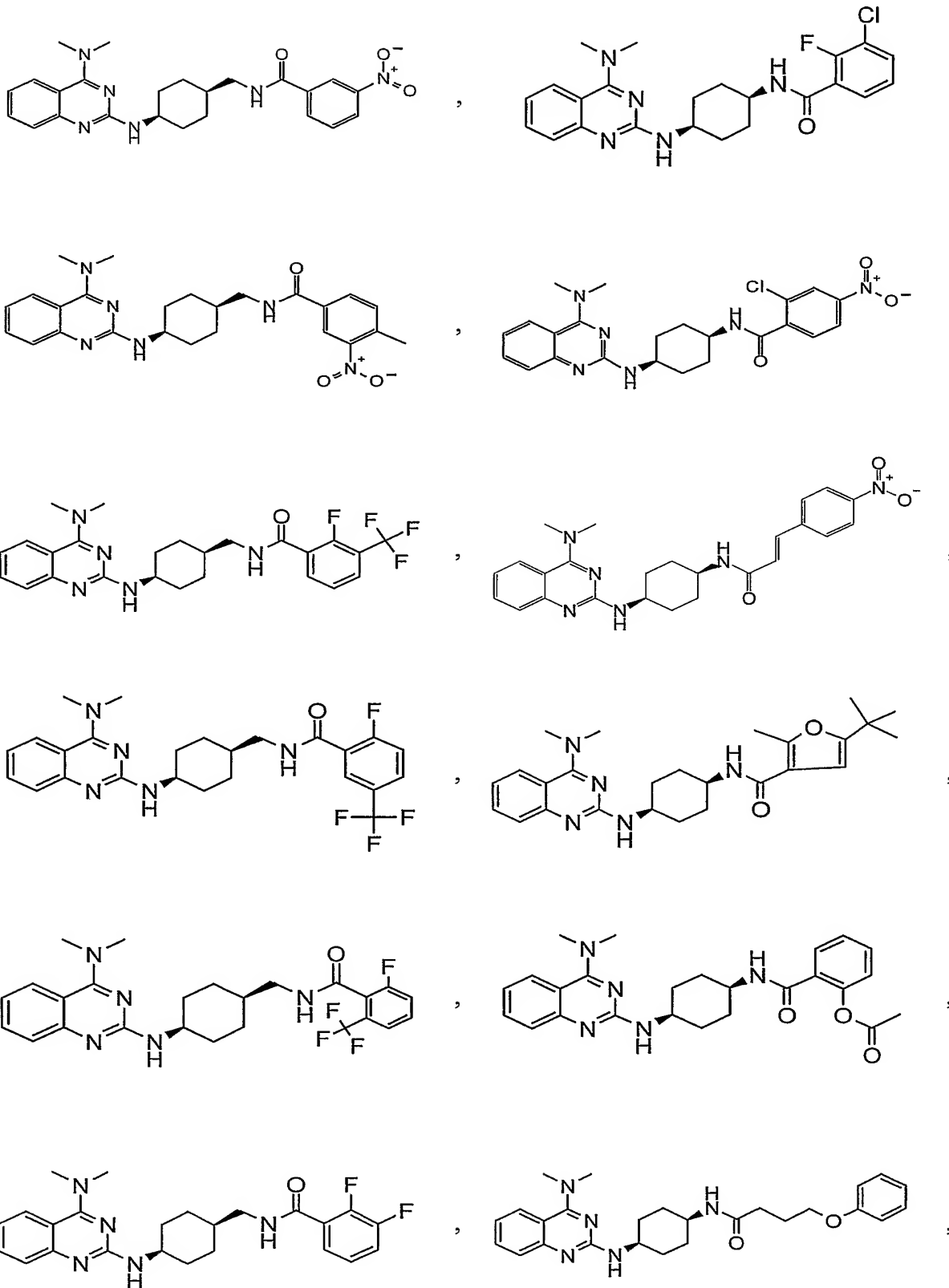
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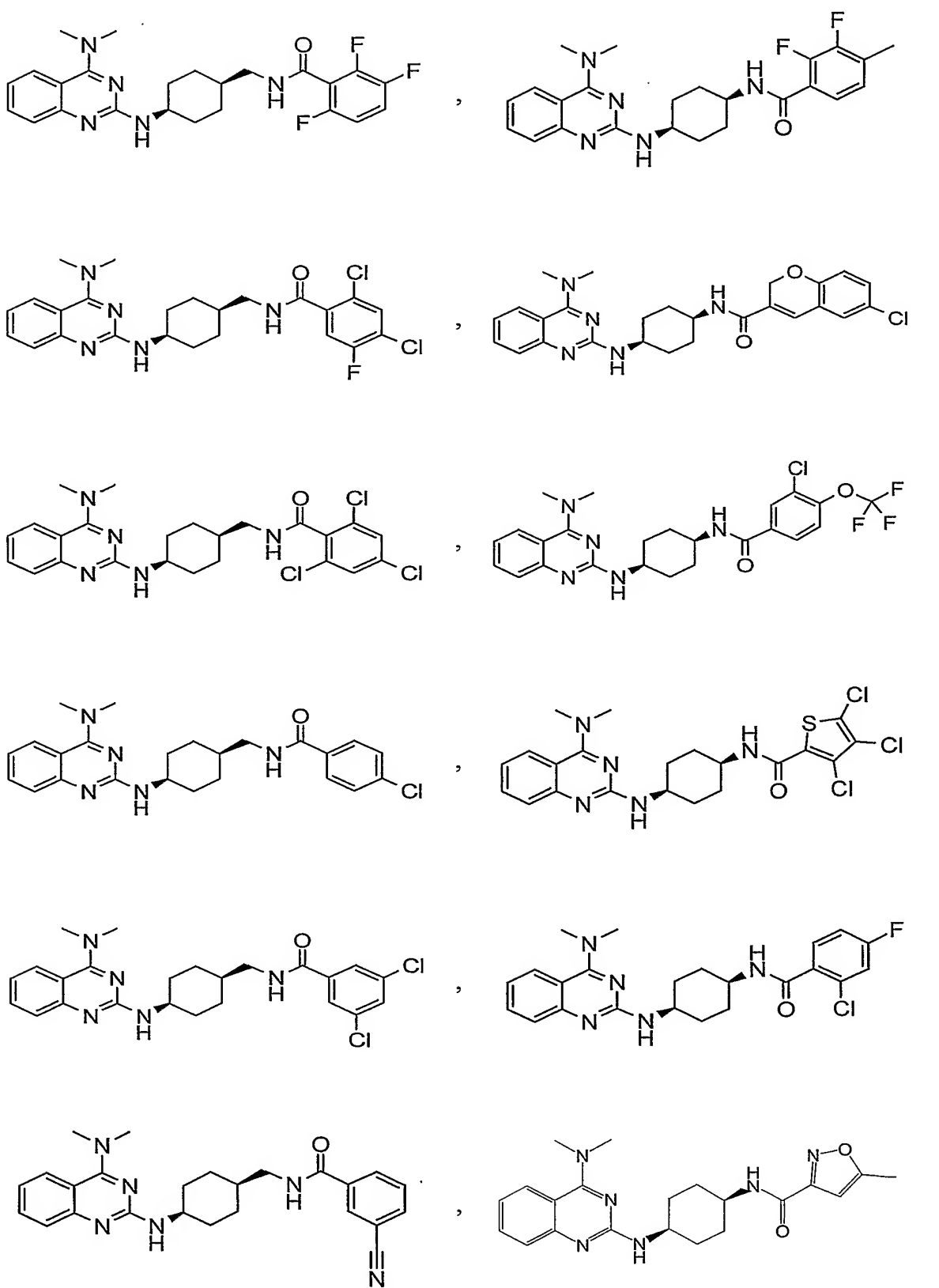


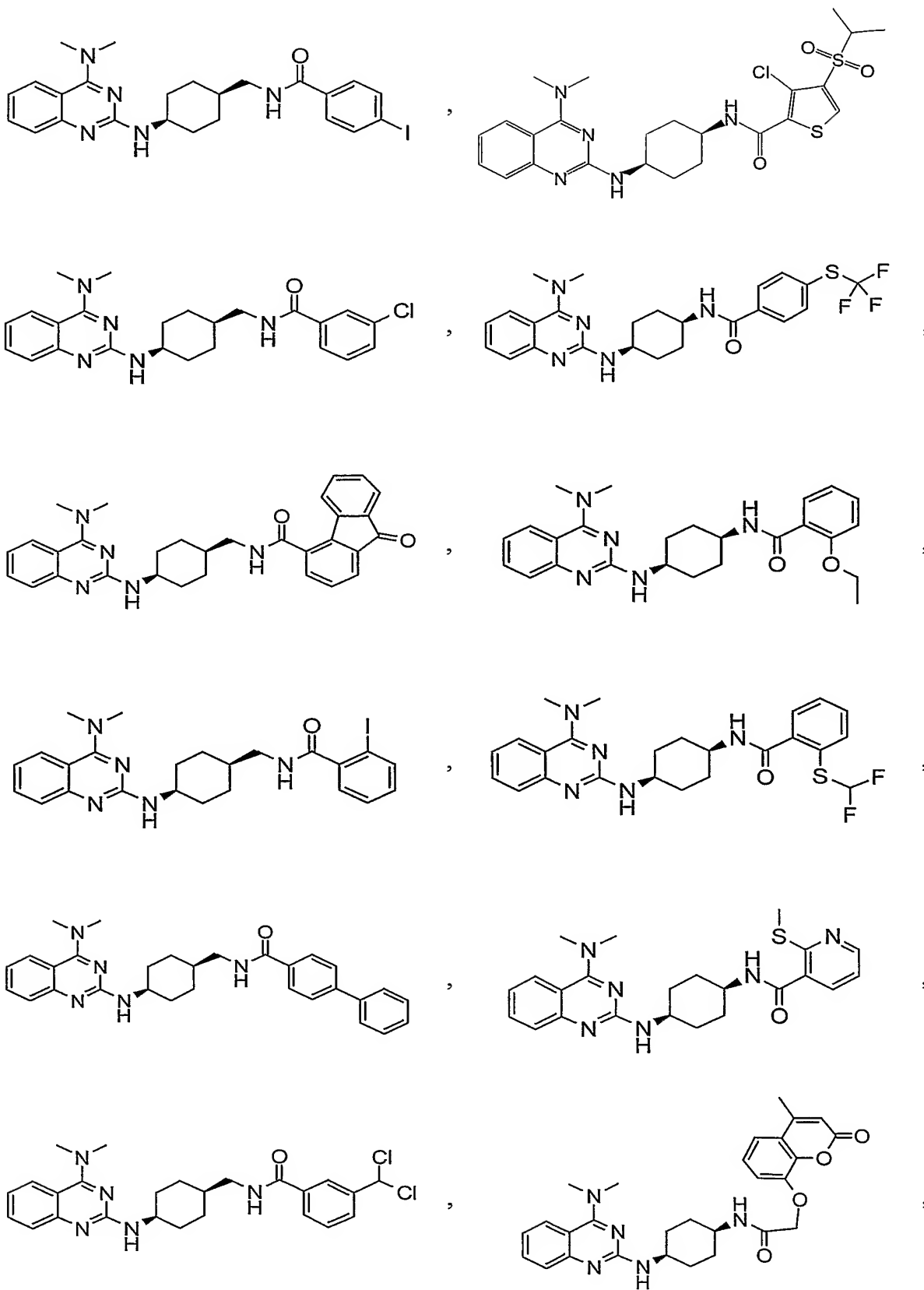


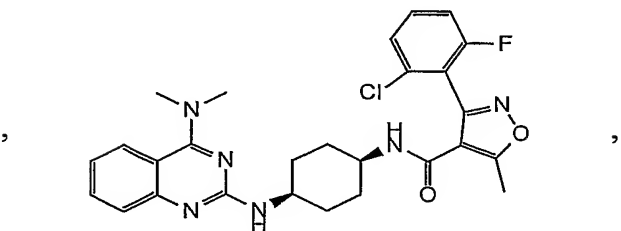
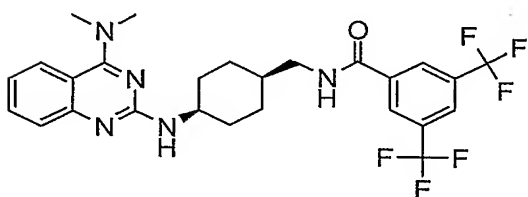
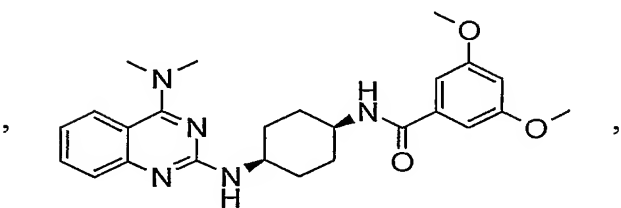
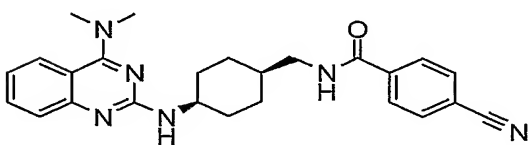
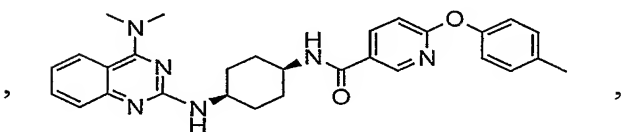
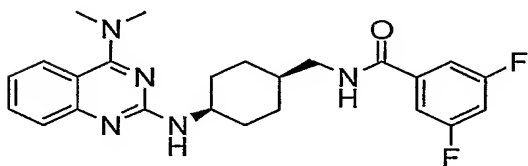
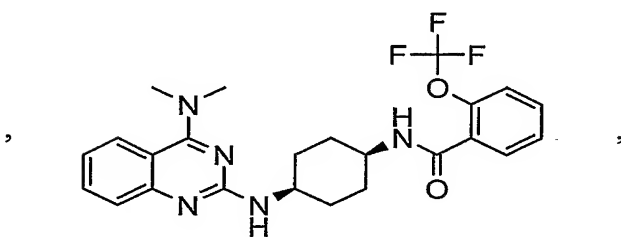
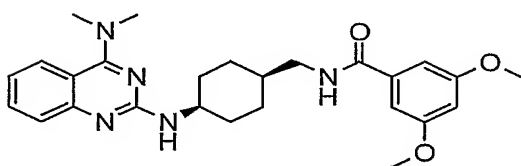
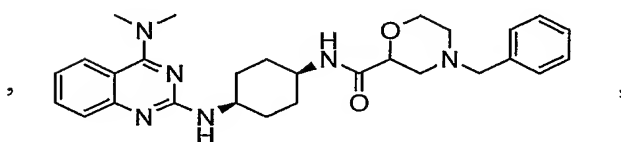
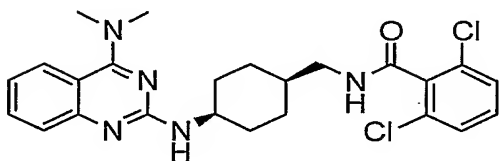
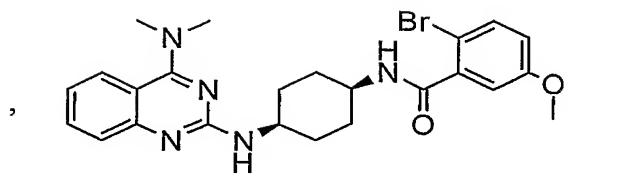
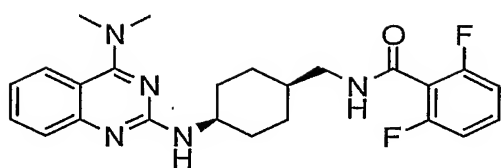


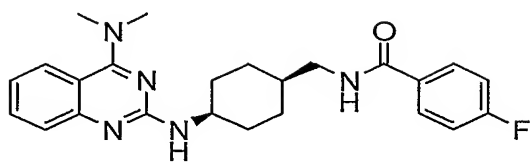




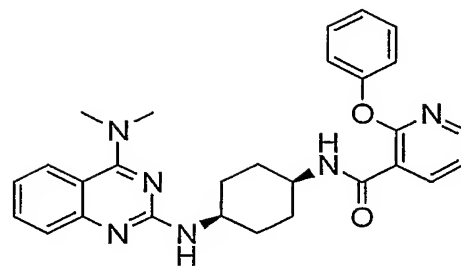




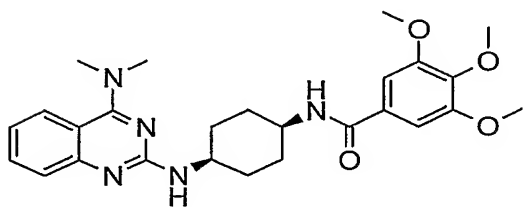




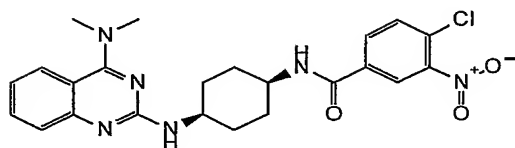
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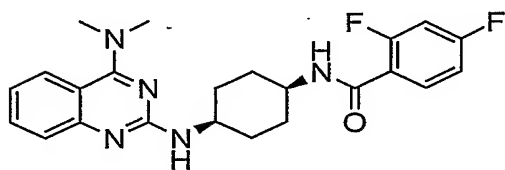
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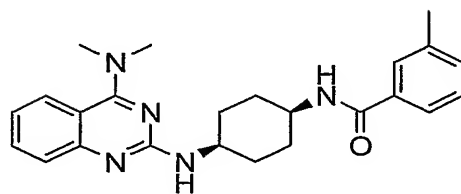
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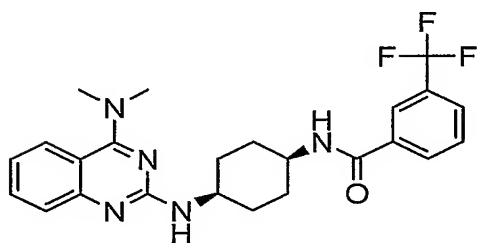
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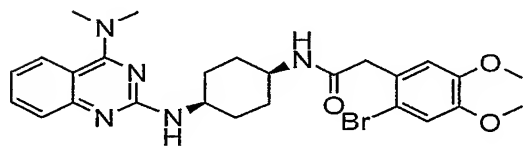
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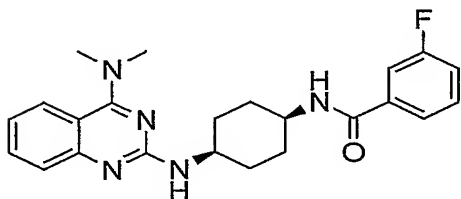
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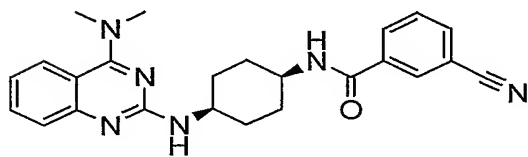
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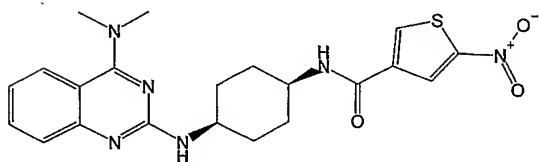
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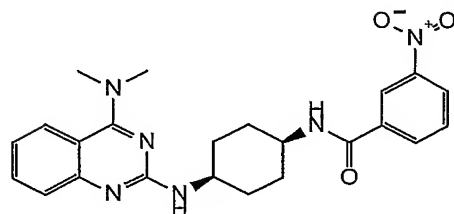
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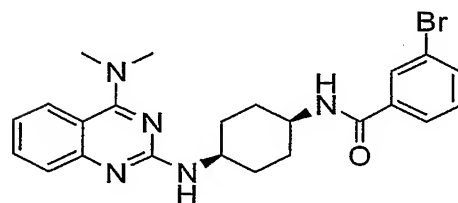
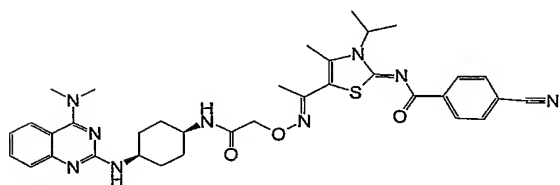
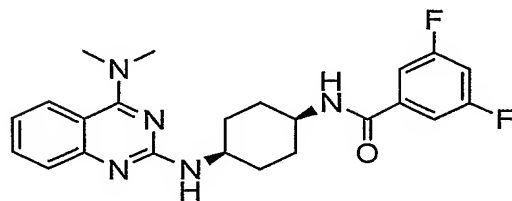
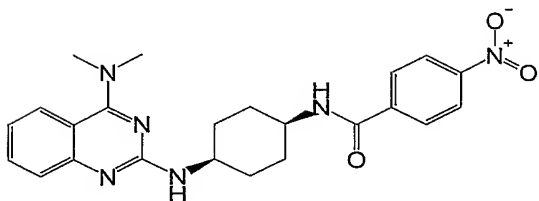
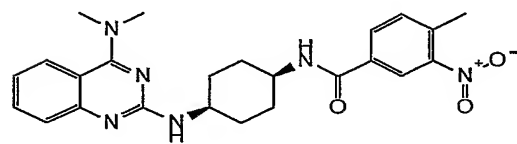
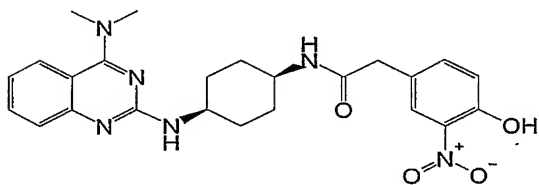
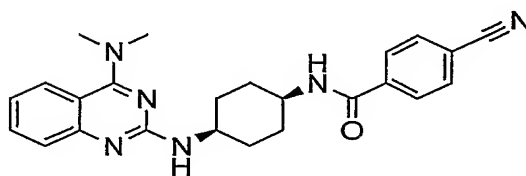
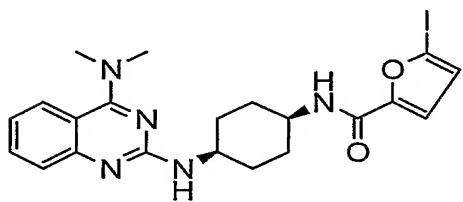
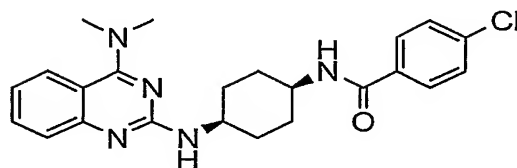
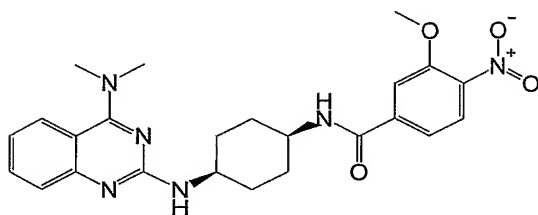
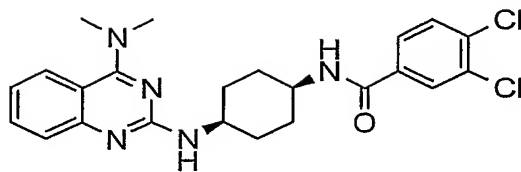
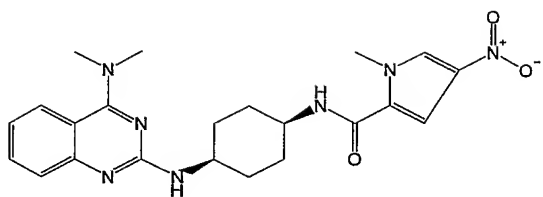
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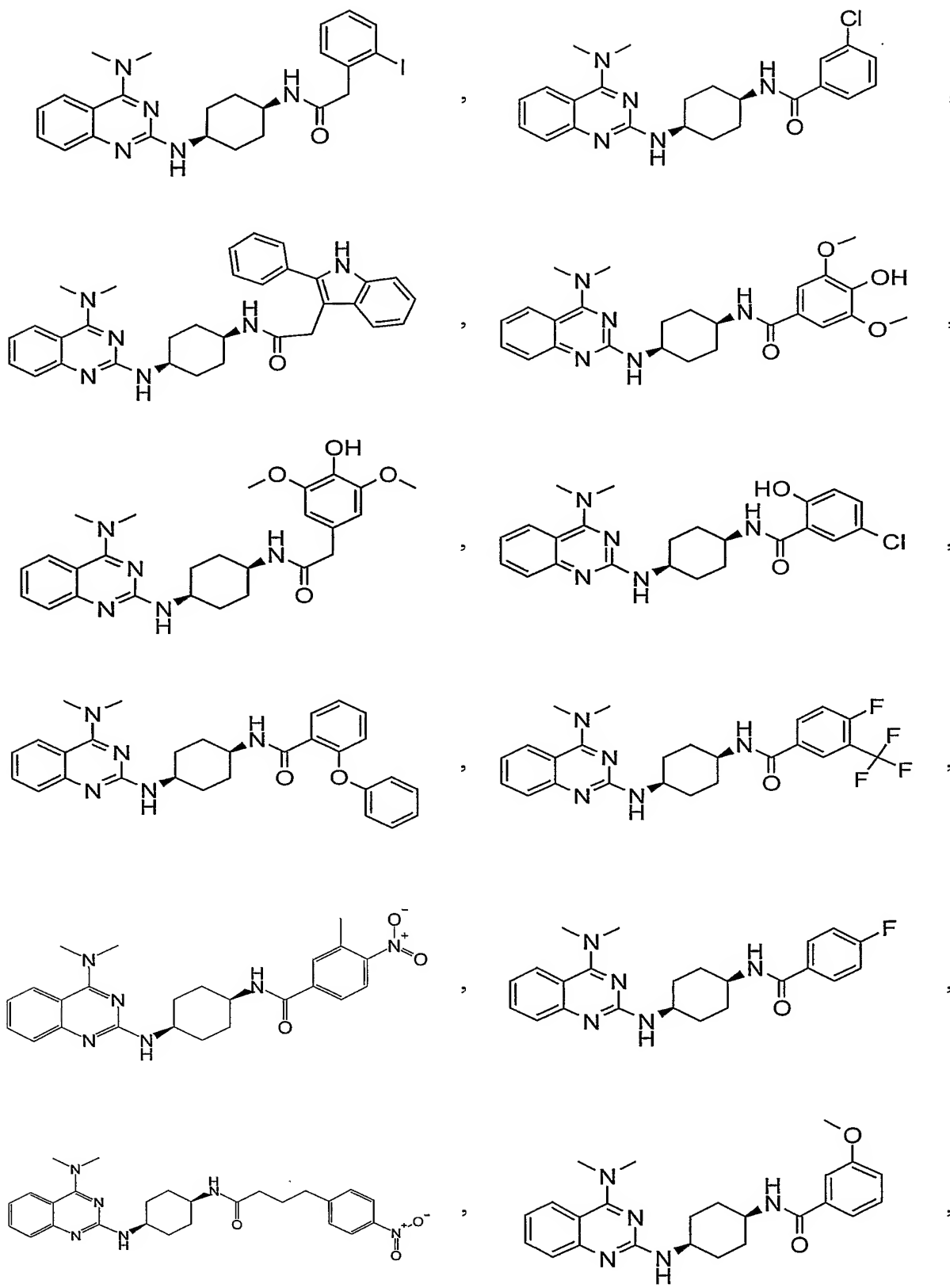


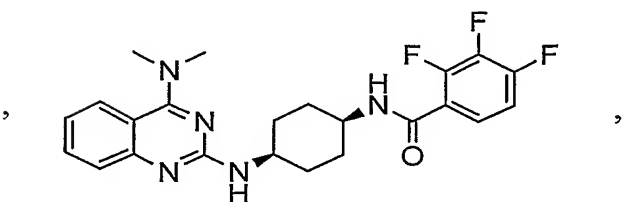
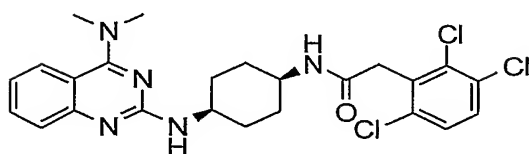
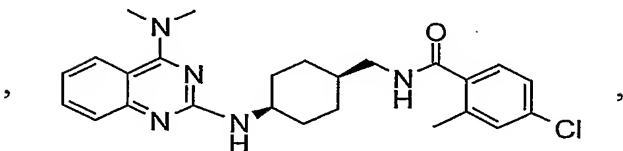
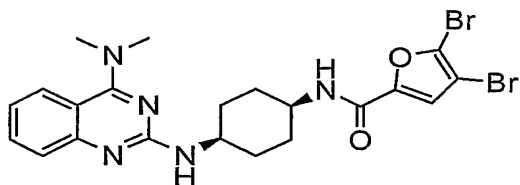
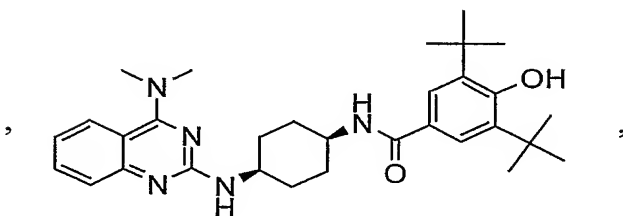
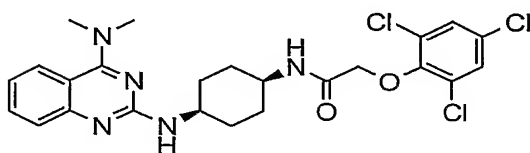
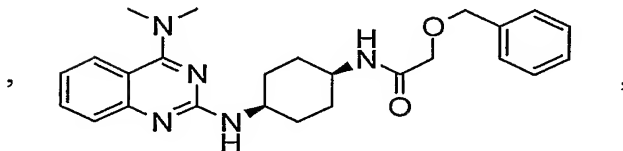
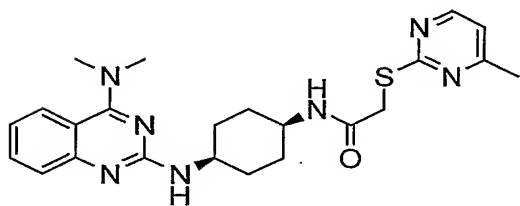
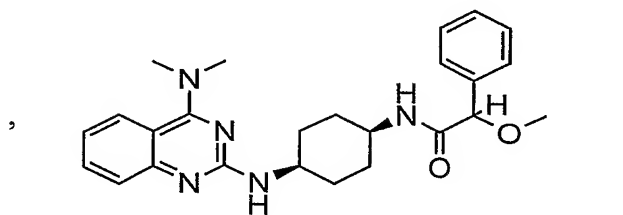
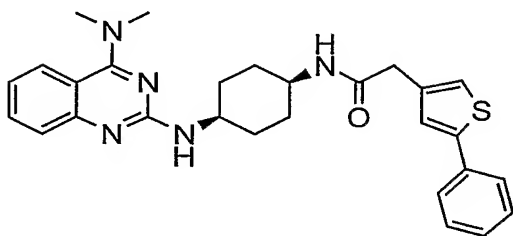
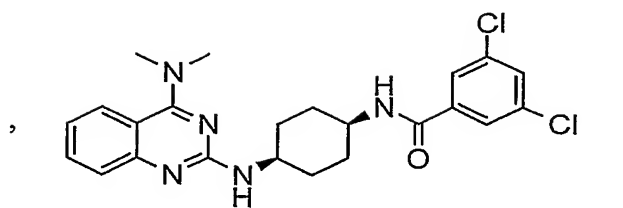
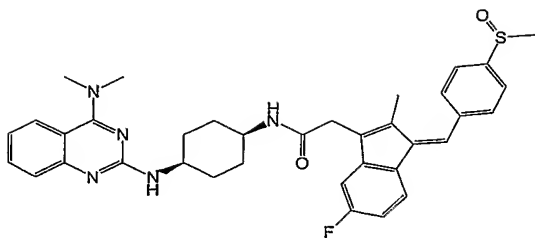
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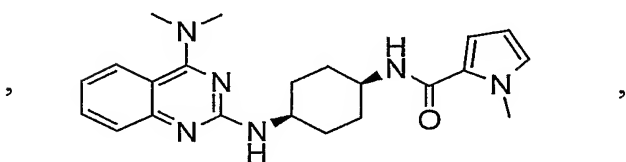
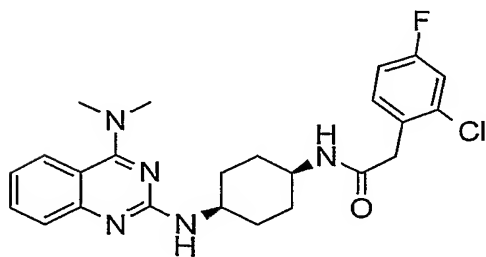
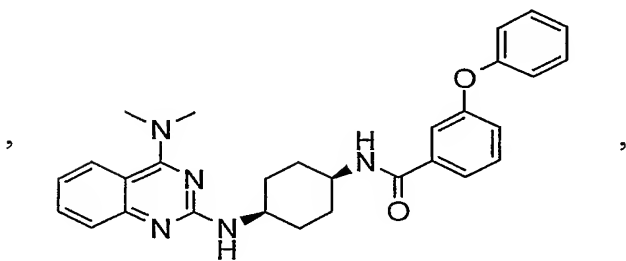
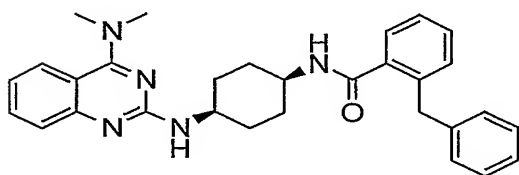
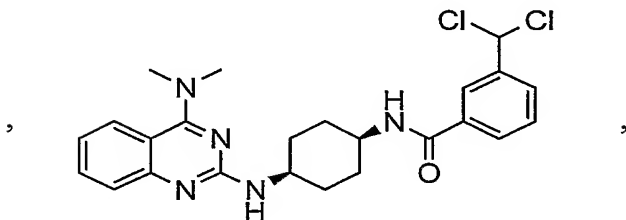
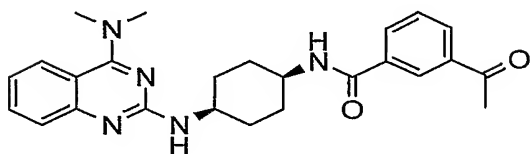
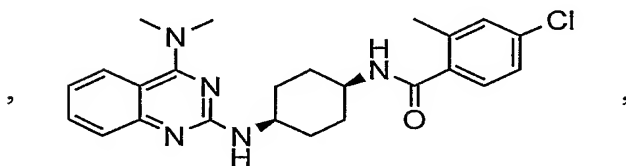
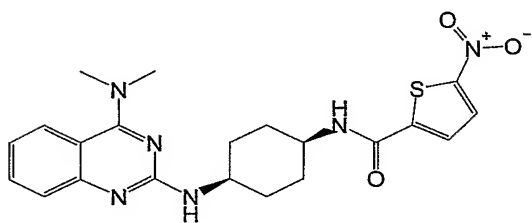
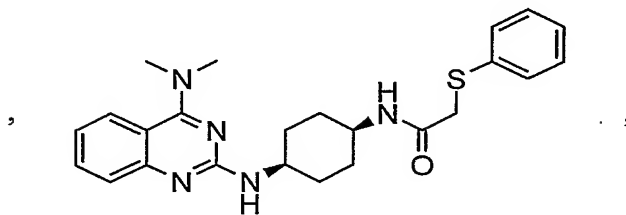
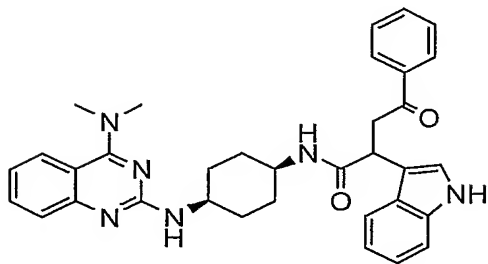
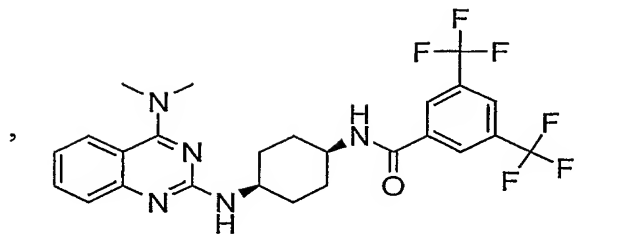
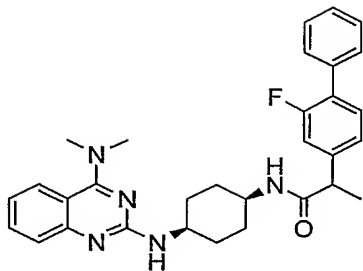


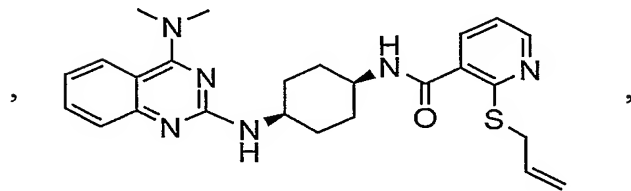
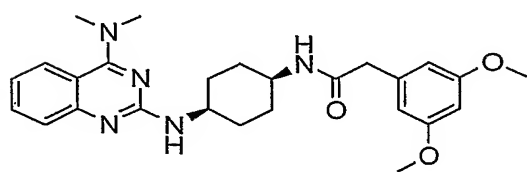
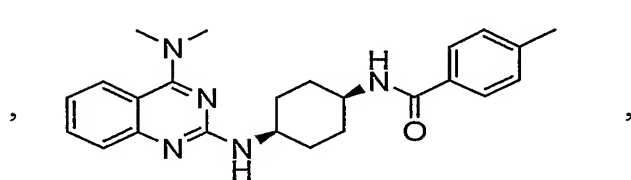
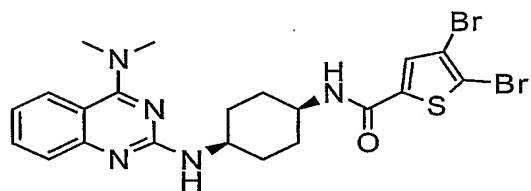
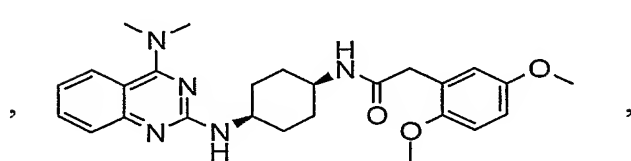
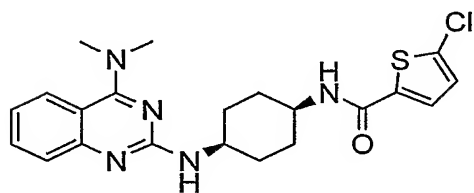
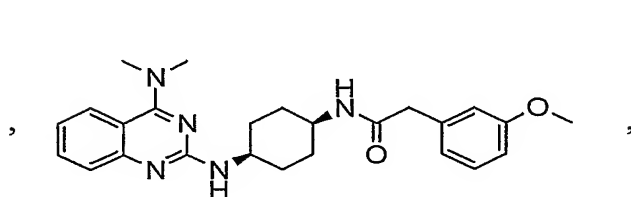
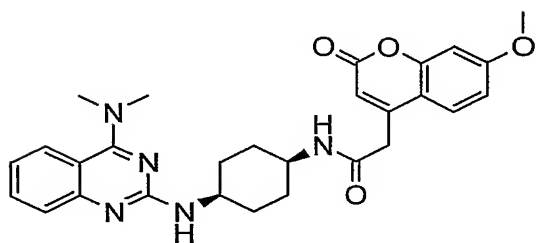
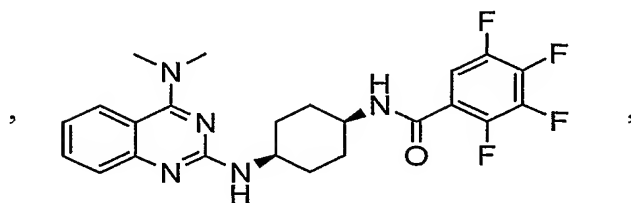
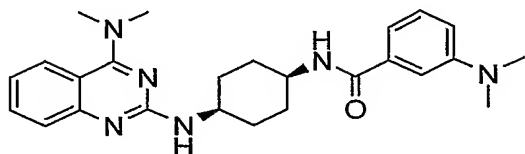
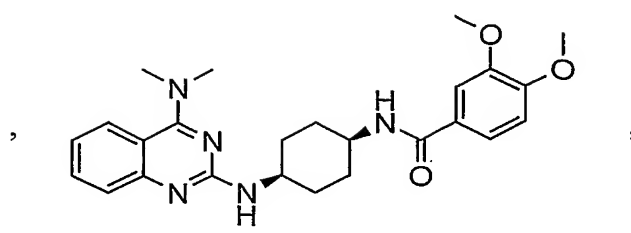
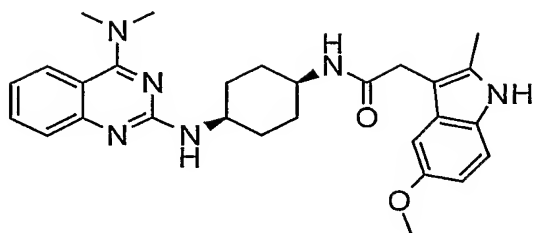
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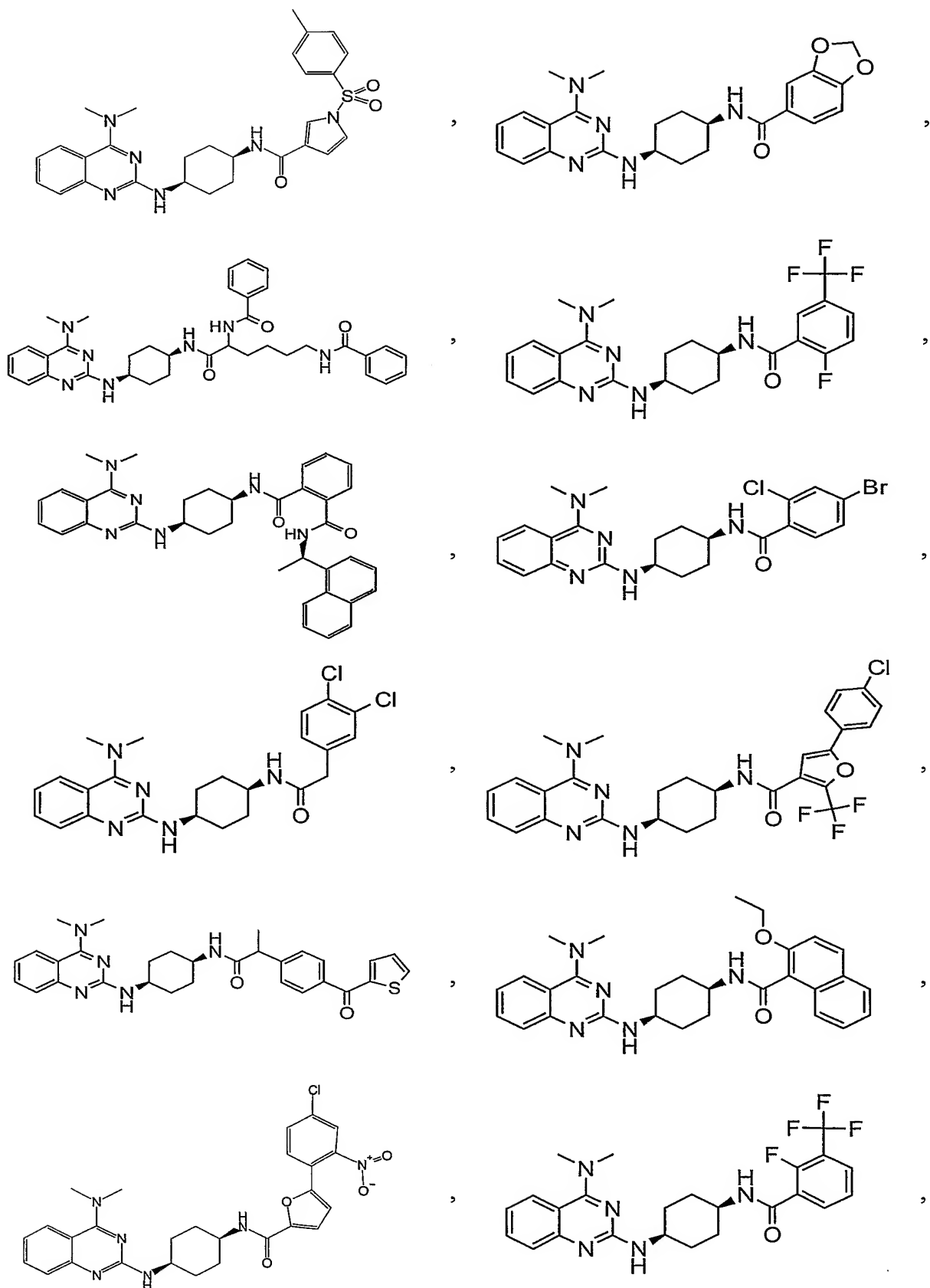


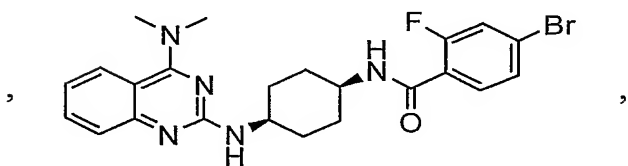
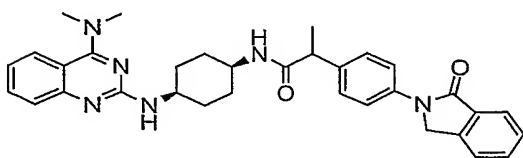
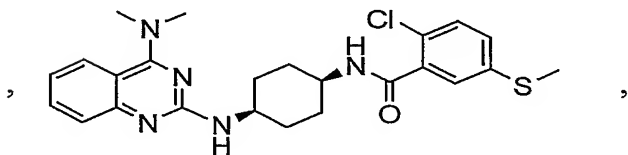
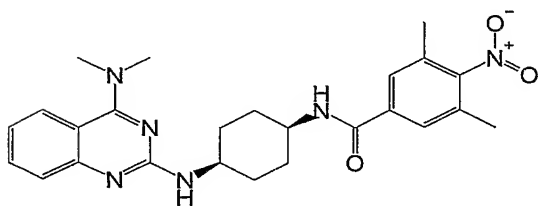
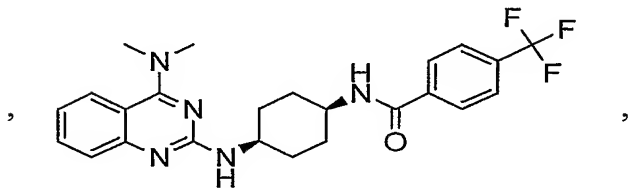
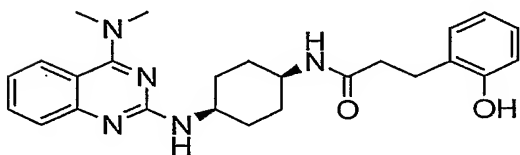
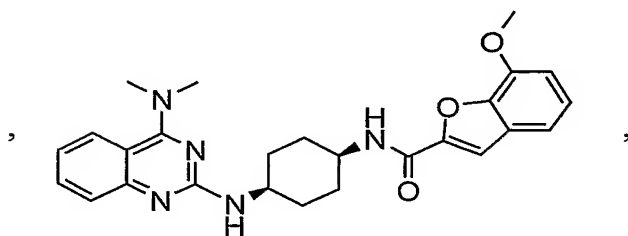
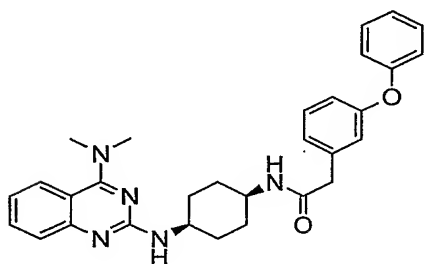
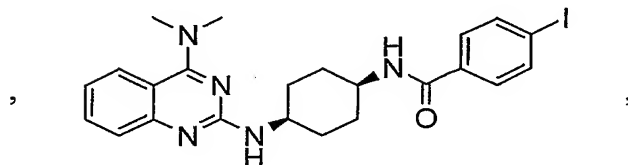
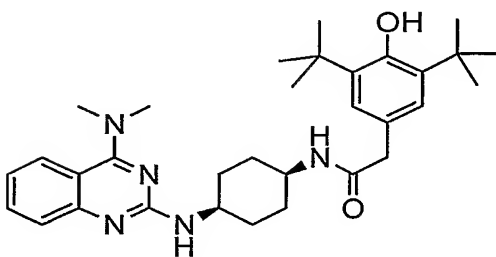
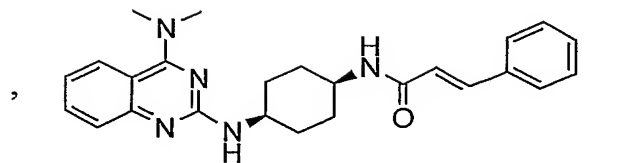
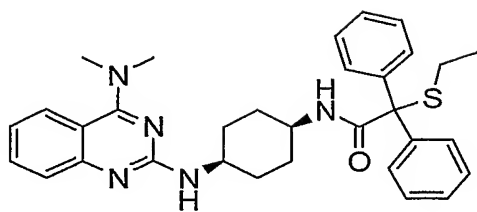


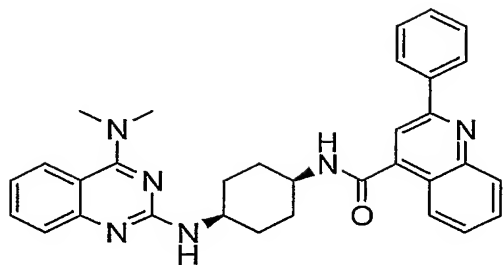




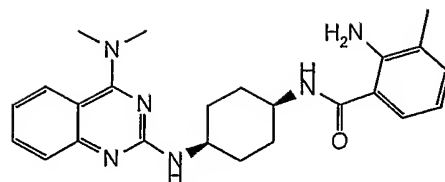




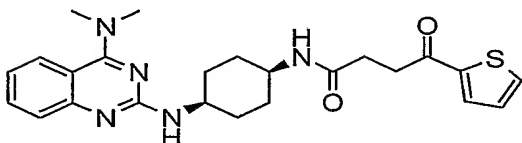




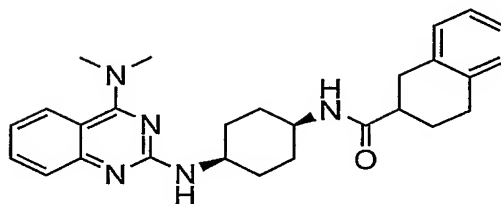
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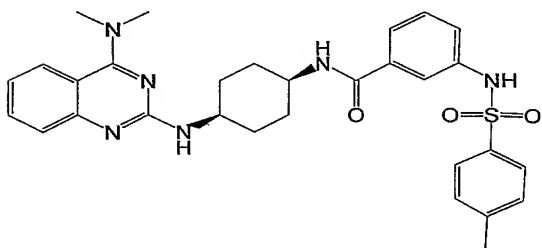
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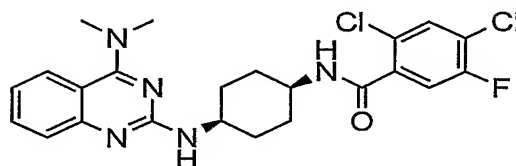
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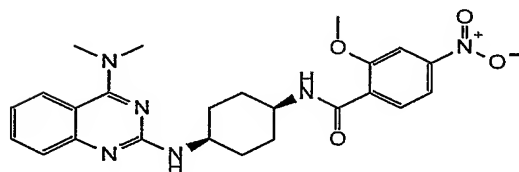
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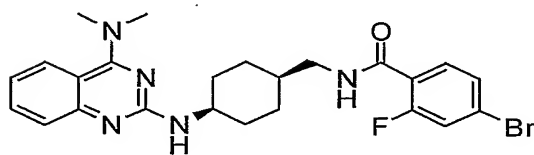
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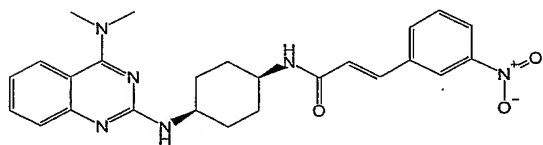
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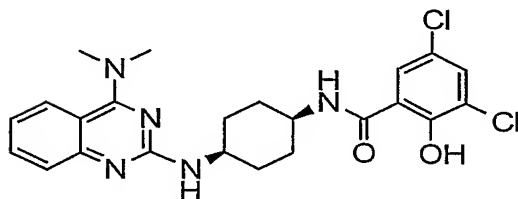
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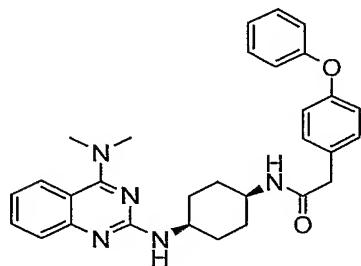
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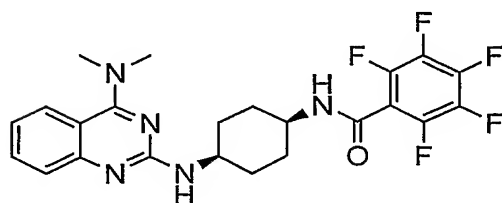
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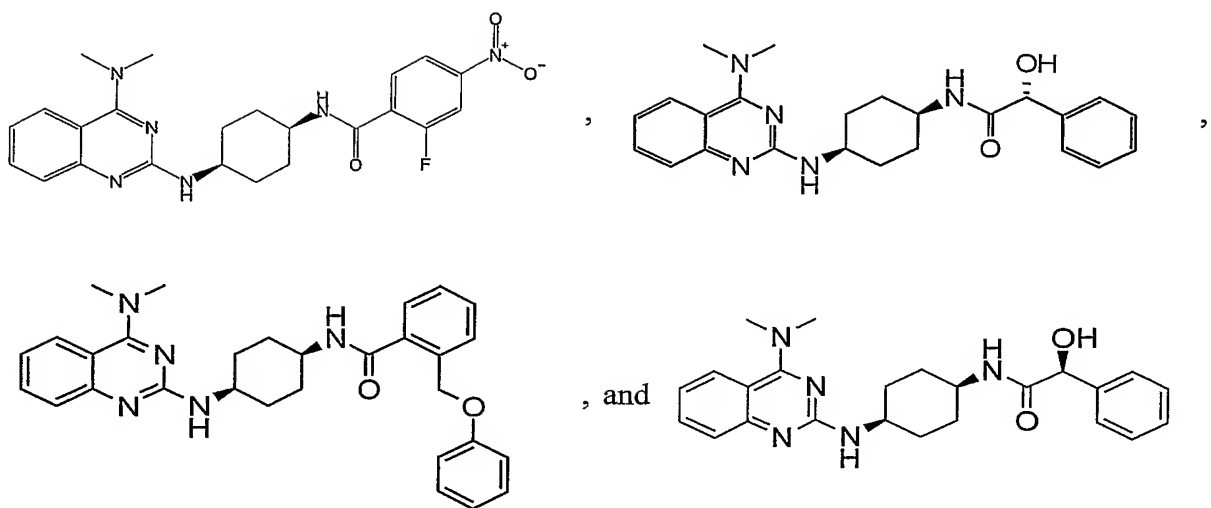
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,



,



; or, in case of, a salt thereof.

Other more preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₀ alkyl,

C₁-C₁₀ alkyl substituted by substituent(s) independently selected from

•C₅-C₆ cycloalkyl,

•carbocyclic aryl,

•heterocyclyl,

(ii) C₃-C₆ cycloalkyl,

(iii) carbocyclic aryl,

(iv) or heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula XX - XXII;

Y is -C(O)-;

wherein carbocyclic aryl is phenyl, naphthyl, anthranyl, or biphenyl;

heterocyclyl is 1,3-dioxo-isoindolyl, 1*H*-indolyl, 1-oxo-3*H*-isobenzofuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, 3,4-dihydro-2*H*-benzo[b][1,4]dioxepinyl, 4-oxo-3,4-dihydro-phthalazinyl, 9,10,10-trioxo-thioxanthenyl, 9*H*-xanthenyl, benzimidazolyl, benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[b]thienyl, furyl, imidazolyl, isoxazolyl, morpholino, oxolanyl, piperidyl, pyridyl, quinoxalyl, thienyl, quinolyl, or benzothiazolyl; halogen is fluoro, chloro, bromo, or iodo.

Further other more preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₄ alkyl,

C₁-C₄ alkyl substituted by substituent(s) independently selected from

•cyclopentyl,

•carbocyclic aryl,

•heterocyclyl,

(ii) carbocyclic aryl,

(iii) or heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula XX - XXII;

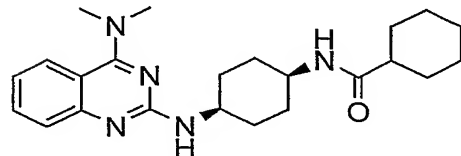
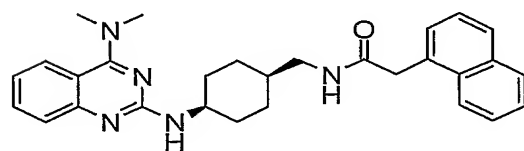
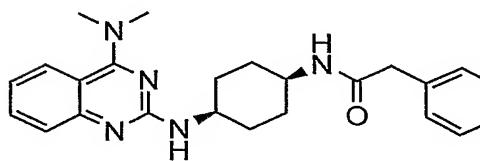
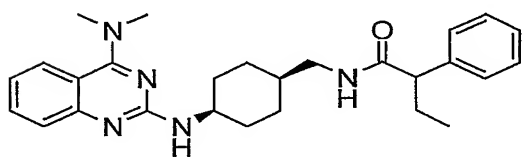
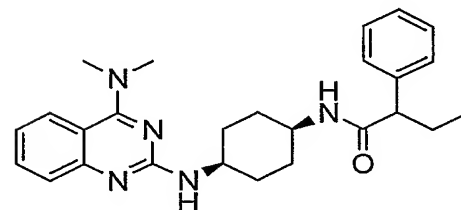
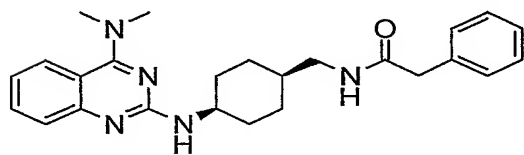
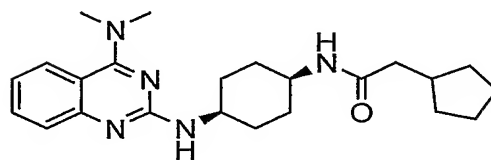
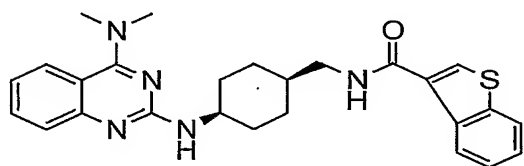
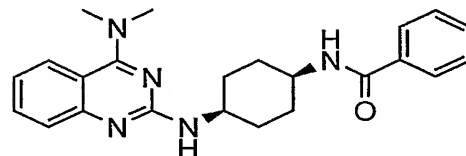
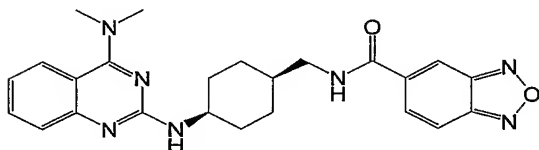
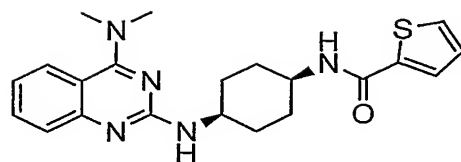
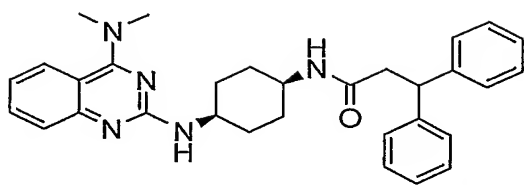
Y is -C(O)-;

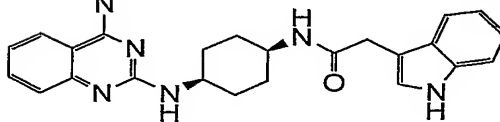
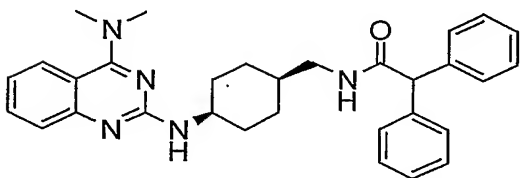
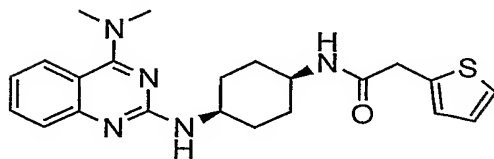
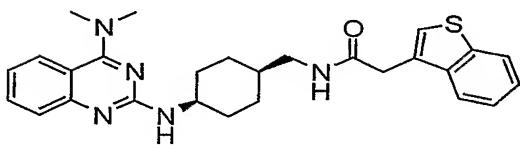
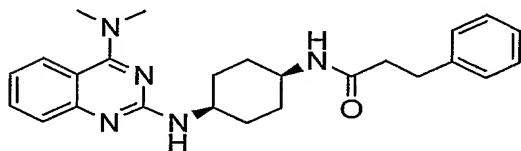
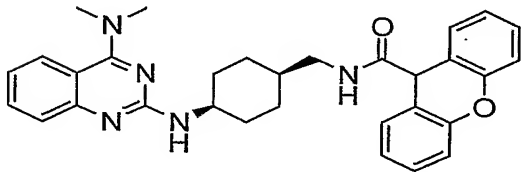
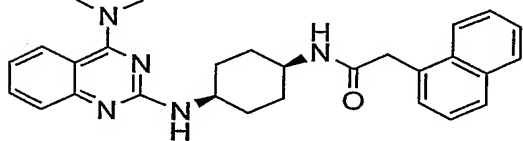
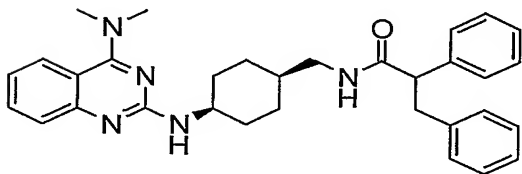
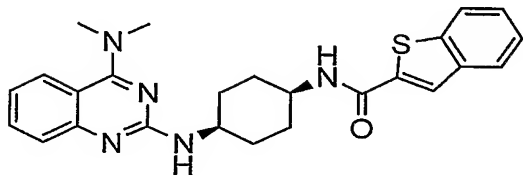
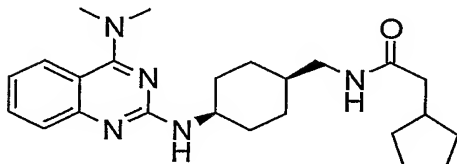
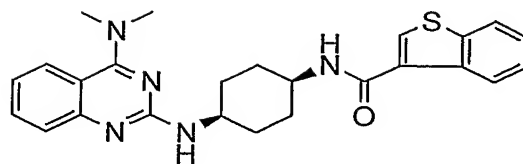
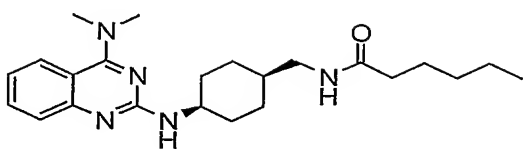
wherein carbocyclic aryl is phenyl, naphthyl, anthranyl, or biphenyl;

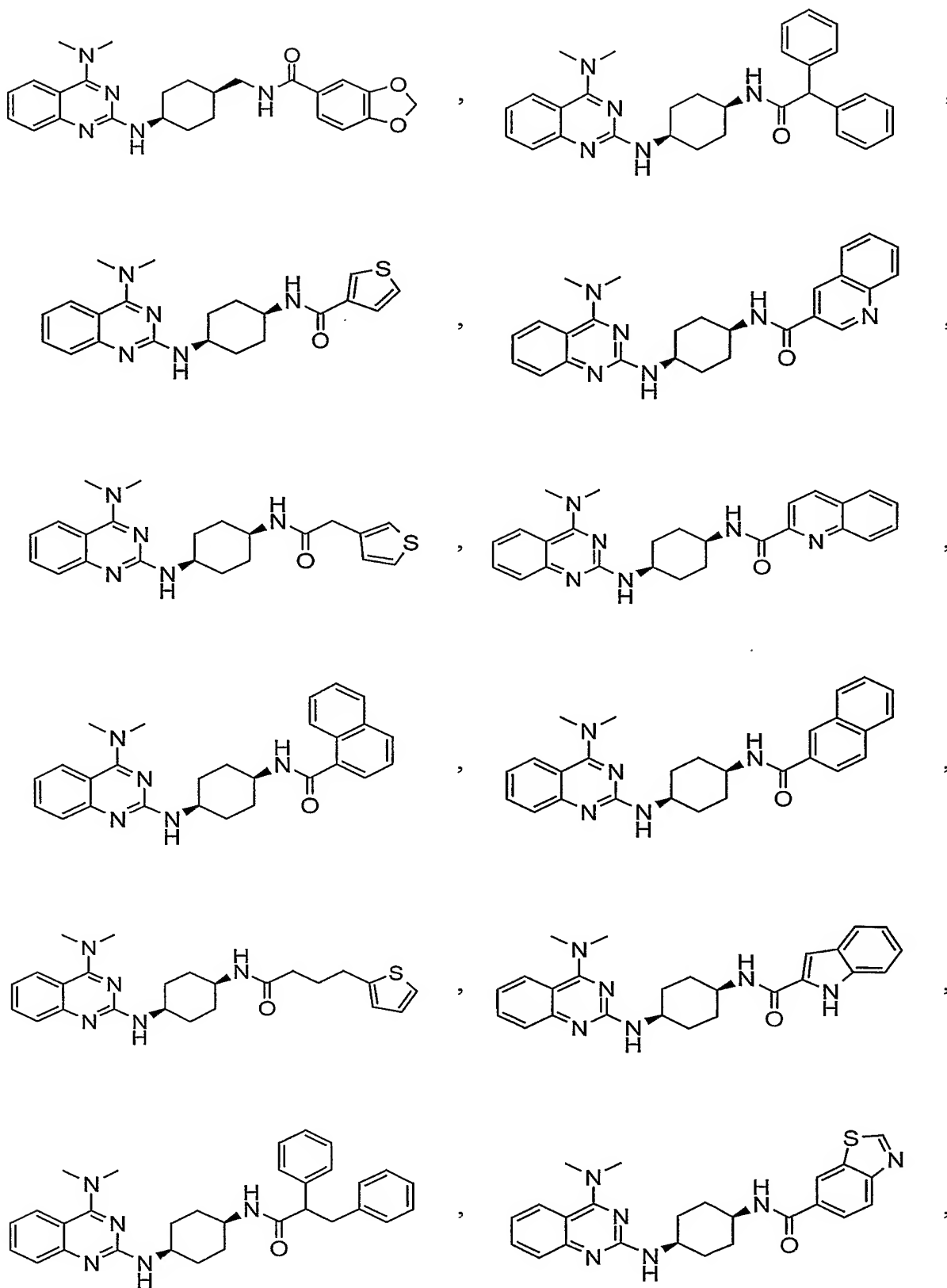
heterocyclyl is 9*H*-xanthenyl, benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[b]thienyl, thienyl, 1*H*-indolyl, quinoxalyl, quinolyl, or benzothiazolyl;

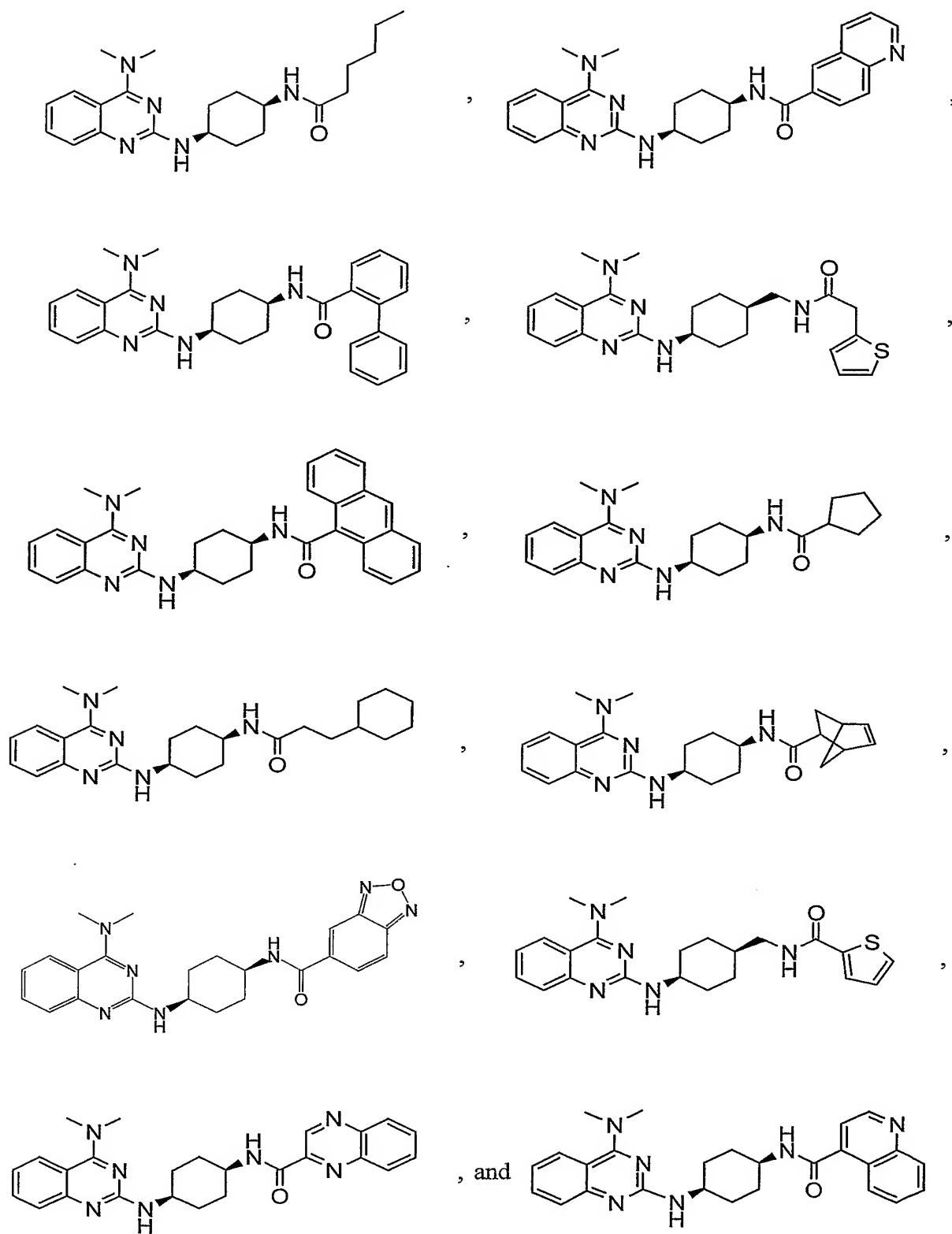
halogen is fluoro, chloro, bromo, or iodo.

The following compounds are specially preferred;









; or, in case of, a salt thereof.

Preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₀ alkyl,

C₁-C₁₀ alkyl substituted by substituent(s) independently selected from

•halogen,

•hydroxy,

•oxo,

•C₁-C₃ alkoxy,

•C₁-C₃ alkoxy substituted by substituent(s) independently selected from

••carbocyclic aryl,

••heterocyclyl,

••heterocyclyl substituted by C₁-C₃ alkyl,

•carbocyclic aryloxy,

•carbocyclic aryloxy substituted by substituent(s) independently selected from

••halogen,

••nitro,

••carbocyclic aryl,

••carbocyclic aryl substituted by C₁-C₃ alkoxy,

••C₁-C₄ alkyl,

••C₁-C₄ alkyl substituted by substituent(s) independently selected from

•••mono- or di-C₁-C₃ alkylamino,

•••mono- or di-C₁-C₃ alkylamino substituted by carbocyclic aryl,

•••mono- or di-C₁-C₃ alkylamino substituted by halogenated carbocyclic aryl,

•mono- or di-C₁-C₃ alkylamino,

•mono- or di-C₁-C₃ alkylamino substituted by substituent(s) independently selected from

••cyano,

••carbocyclic aryl,

••heterocyclyl,

•mono- or di-carbocyclic arylamino,

•mono- or di-carbocyclic arylamino substituted by C₁-C₃ alkyl,

•C₁-C₃ alkylcarbonylamino,

- C₁-C₄ alkoxycarbonylamino,
- carbocyclic arylsulfonylamino,
- carbocyclic arylsulfonylamino substituted by substituent(s) independently selected from
 - nitro,
- C₁-C₃ alkyl,
- mono- or di-C₁-C₃ alkylamino,
- C₁-C₃ alkylthio,
- C₁-C₃ alkylthio substituted by substituent(s) independently selected from
 - mono- or di-carbocyclic arylamino,
 - halogenated mono- or di-carbocyclic arylamino,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkoxy,
- carbocyclic arylthio,
- carbocyclic arylthio substituted by substituent(s) independently selected from
 - halogen,
- C₁-C₃ alkyl,
- carbocyclic arylsulfonyl,
- halogenated carbocyclic arylsulfonyl,
- heterocyclylthio,
- C₃-C₆ cycloalkyl,
- C₃-C₆ cycloalkyl substituted by C₁-C₃ alkyl,
- carbocyclyl,
- carbocyclyl substituted by substituent(s) independently selected from
 - halogen,
- C₁-C₃ alkyl,
- C₂-C₃ alkenyl,
- C₂-C₃ alkenyl substituted by carbocyclic aryl,
- C₂-C₃ alkenyl substituted by carbocyclic aryl substituted C₁-C₃ alkylsulfinyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,
- hydroxy,
- nitro,
- C₁-C₄ alkyl,
- C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - carbocyclic aryl,
 - mono- or di-carbocyclic arylamino,
 - mono- or di-carbocyclic arylamino substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - halogenated C₁-C₃ alkoxy,
- C₁-C₃ alkoxy,
- C₁-C₃ alkoxy substituted by substituent(s) independently selected from
 - halogen,
 - carbocyclic aryl,
 - carbocyclic aryloxy,
 - C₁-C₃ alkoxycarbonyl,
 - mono- or di-C₁-C₃ alkylamino,
 - C₁-C₃ alkylthio,
 - halogenated C₁-C₃ alkylthio,
 - C₁-C₃ alkylsulfonyl,
 - C₃-C₆ cycloalkyl,
 - carbocyclic aryl,
 - heterocyclyl,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,

- C₁-C₃ alkoxy,
- C₁-C₃ alkoxy substituted by carbocyclic aryl,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- (ii) C₂-C₈ alkenyl,
- C₂-C₈ alkenyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkoxy,
 - C₁-C₃ alkoxy substituted by carbocyclic aryl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - C₁-C₃ alkoxy,
 - halogenated C₁-C₃ alkoxy,
 - heterocyclyl,
 - heterocyclyl substituted by nitro,
- (iii) C₂-C₄ alkynyl,
- C₂-C₄ alkynyl substituted by carbocyclic aryl,
- (iv) C₃-C₆ cycloalkyl,
- C₃-C₆ cycloalkyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,
 - C₁-C₃ alkyl substituted by substituent(s) independently selected from
 - hydroxy,
 - oxo,
 - carbocyclic aryl,
 - mono- or di-C₁-C₃ alkylamino,
 - mono- or di-C₁-C₃ alkylamino substituted by carbocyclic aryl,
 - carbocyclic aryl,
- (v) C₃-C₆ cycloalkenyl,
- C₃-C₆ cycloalkenyl substituted by C₁-C₃ alkyl,
- (vi) carbocyclyl,

carbocyclyl substituted by substituent(s) independently selected from

- hydroxy,

- nitro,

(vii) carbocyclic aryl,

carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,

- hydroxy,

- cyano,

- nitro,

- C₁-C₉ alkyl,

- C₁-C₉ alkyl substituted by substituent(s) independently selected from

- halogen,

- hydroxy,

- oxo,

- C₁-C₃ alkoxy,

- carbocyclic aryloxy,

- mono- or di-C₁-C₃ alkylamino-N-oxy,

- mono- or di-C₁-C₃ alkylamino,

- mono- or di-C₁-C₃ alkylamino substituted by carbocyclic aryl,

- mono- or di-carbocyclic arylamino,

- mono- or di-carbocyclic arylamino substituted by C₁-C₃ alkoxy,

- carbocyclic aryl,

- halogenated carbocyclic aryl,

- heterocyclyl,

- heterocyclyl substituted by C₁-C₃ alkyl,

- C₂-C₃ alkenyl,

- C₂-C₃ alkenyl substituted by carbocyclic aryl,

- C₁-C₉ alkoxy,

- C₁-C₉ alkoxy substituted by substituent(s) independently selected from

- hydroxy,

- halogen,

- carboxy,

- mono- or di-C₁-C₃ alkylamino,
- carbocyclic aryl,
- halogenated carbocyclic aryl,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- C₂-C₃ alkenyloxy,
- C₁-C₃ alkylcarbonyloxy,
- carbocyclic aryloxy,
- carbocyclic aryloxy substituted by substituent(s) independently selected from
- halogen,
- C₁-C₄ alkyl,
- halogenated C₁-C₄ alkyl,
- C₁-C₃ alkoxy,
- heterocyclyloxy,
- heterocyclyloxy substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- (carbocyclic aryl)S(O)₂O,
- carboxy,
- C₁-C₃ alkoxycarbonyl,
- mono- or di-C₁-C₃ alkylaminocarbonyl,
- mono- or di-C₁-C₃ alkylaminocarbonyl substituted by carbocyclic aryl,
- amino,
- mono- or di-C₁-C₄ alkylamino,
- mono- or di-C₁-C₄ alkylamino substituted by cyano,
- mono- or di-carbocyclic arylamino,

- C₁-C₃ alkylcarbonylamino,
- carbocyclic arylsulfonylamino,
- carbocyclic arylsulfonylamino substituted by C₁-C₃ alkyl,
- (carbocyclic aryl)NHC(O)NH,
- (carbocyclic aryl)NHC(O)NH substituted by C₁-C₃ alkoxy,
- (carbocyclic aryl)NHC(O)NH substituted by halogenated C₁-C₃ alkoxy,
- C₁-C₃ alkylthio,
- halogenated C₁-C₃ alkylthio,
- carbocyclic arylthio,
- halogenated carbocyclic arylthio,
- carbocyclic arylthio substituted by C₁-C₃ alkyl,
- heterocyclylthio,
- C₁-C₃ alkylsulfonyl,
- mono- or di-C₁-C₃ alkylaminosulfonyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - C₁-C₇ alkyl,
 - halogenated C₁-C₇ alkyl,
 - heterocyclyl,
 - heterocyclyl substituted by substituent(s) independently selected from
 - C₁-C₃ alkyl,
 - carbocyclic aryl,
 - halogenated carbocyclic aryl,
- (viii) heterocyclyl,
- or heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by substituent(s) independently selected from
 - halogen,

- hydroxy,
- oxo,
- C₁-C₃ alkylcarbonyloxy,
- C₁-C₃ alkoxy carbonyl,
- C₁-C₃ alkylthio,
- C₁-C₃ alkylthio substituted by carbocyclic aryl,
- C₁-C₃ alkylthio substituted by halogenated carbocyclic aryl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - heterocyclyl,
 - C₁-C₃ alkoxy,
 - C₁-C₃ alkoxy substituted by carbocyclic aryl,
 - carbocyclic aryloxy,
 - carbocyclic aryloxy substituted by C₁-C₃ alkyl,
 - mono- or di-C₁-C₃ alkylamino,
 - C₁-C₄ alkylcarbonylamino,
 - C₁-C₃ alkylthio,
 - carbocyclic arylthio,
 - halogenated carbocyclic arylthio,
 - carbocyclic arylthio substituted by C₁-C₃ alkoxy carbonyl,
 - heterocyclylthio,
 - heterocyclylthio substituted by C₁-C₃ alkyl,
 - C₁-C₃ alkylsulfonyl,
 - carbocyclic arylsulfonyl,
 - carbocyclic arylsulfonyl substituted by C₁-C₄ alkyl,
 - C₁-C₃ alkoxy carbonyl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,

- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- halogenated C₁-C₃ alkoxy,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- C₁-C₃ alkoxycarbonyl;

R₂ is -NHNH₂, -NHNHBoc, -N(R_{2a})(R_{2b}), morpholino, 4-acetyl-piperazyl, or 4-phenyl-piperazyl;

wherein R_{2a} is H or C₁-C₃ alkyl;

R_{2b} is C₁-C₄ alkyl, C₁-C₄ alkyl substituted by substituent(s) independently selected from

- hydroxy,
- C₁-C₃ alkoxy,
- amino,
- NHBoc,
- C₃-C₆ cycloalkyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- SO₂NH₂,
- heterocyclyl,

C₃-C₆ cycloalkyl, carbocyclic aryl, carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,
- C₁-C₃ alkyl,
- C₁-C₃ alkoxy,

or a group of Formula IV;

wherein Boc is carbamic acid *tert*-butyl ester and R₃ is C₁-C₃ alkyl or C₁-C₃ alkyl substituted by substituent(s) independently selected from

- carbocyclic aryl,
- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by C₁-C₃ alkoxy;

L is selected from Formula V - XIX;

wherein R₄ is H or C₁-C₃ alkyl;

R₅ is H, C₁-C₃ alkyl, or C₁-C₃ alkyl substituted by a substituted carbocyclic aryl;

Y is -(CH₂)_m, m is 0 or 1;

wherein carbocyclic aryl is phenyl, naphthyl, phenanthryl, or biphenyl;

carbocyclyl is 9*H*-fluorenyl, 9-oxo-fluorenyl, acenaphthyl, anthraquinonyl, indanyl, or indenyl;

heterocyclyl is 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,2-dihydro-3-oxo-pyrazolyl, 1,3,4-thiadiazolyl, 1,3-dioxo-isoindolyl, 1,3-dioxolanyl, 1*H*-indolyl, 1*H*-pyrrolo[2,3-*c*]pyridyl, 1*H*-pyrrolyl, 2,2',5',2"-terthiophenyl, 2,2'-bithiophenyl, 2,3-dihydro-1-oxo-isoindolyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2,3-dihydro-benzofuryl, 2,4-dihydro-3-oxo-pyrazolyl, 2*H*-benzopyranyl, 2-oxo-pyrrolidinyl, 3,4-dihydro-2*H*-benzo[1,4]oxazinyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepinyl, 4*H*-benzo[1,3]dioxinyl, 4*H*-benzopyranyl, 4-oxo-1,5,6,7-tetrahydro-indolyl, 4-oxo-benzopyranyl, 9*H*-carbazolyl, 9*H*-xanthenyl, azetidiny, benzimidazolyl, benzo[1,3]dioxolyl, benzo[*b*]thienyl, benzofuryl, benzothiazolyl, furyl, imidazo[2,1-*b*]thiazolyl, imidazolyl, isoxazolyl, morpholino, morpholinyl, oxolanyl, piperazyl, piperidyl, pyrazolo[5,1-*b*]thiazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolidyl, quinolyl, quinoxalyl, thiazolidyl, thiazolyl, thienyl, or thiolanyl;

halogen is fluoro, chloro, bromo, or iodo.

Other preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₀ alkyl substituted by substituent(s) independently selected from

- methoxy,
- methoxy substituted by carbocyclic aryl,

- carbocyclic aryloxy,
- halogenated carbocyclic aryloxy,
- mono-C₁-C₂ alkylamino substituted by cyano,
- mono- or di-C₁-C₂ alkylamino substituted by carbocyclic aryl,
- mono-carbocyclic arylamino,
- mono-carbocyclic arylamino substituted by methyl,
- carbocyclic arylsulfonylamino substituted by methyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by carbocyclic aryl,
 - C₁-C₄ alkyl substituted by hydroxy,
 - C₁-C₂ alkoxy,
 - halogenated C₁-C₂ alkoxy,
 - heterocyclyl substituted by carbocyclic aryl,
- (ii) C₂-C₈ alkenyl substituted by substituent(s) independently selected from
 - methoxy substituted by carbocyclic aryl,
 - carbocyclic aryl,
 - carbocyclic aryl substituted by methoxy,
- (iii) C₂-C₄ alkynyl substituted by carbocyclic aryl,
- (iv) cyclohexyl substituted by carbocyclic arylmethyl,
- (v) carbocyclyl,
- (vi) carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - hydroxy,
 - cyano,
 - amino,
 - C₁-C₉ alkyl,
 - halogenated C₁-C₉ alkyl,

- C₁-C₉ alkoxy,
- C₁-C₉ alkoxy substituted by substituent(s) independently selected from
- halogen,
- halogenated carbocyclic aryl,
- propenyloxy,
- methylamino,
- di-C₁-C₂ alkylamino,
- di-C₁-C₂ alkylamino substituted by cyano,
- methylthio,
- halogenated methylthio,
- (vii) heterocyclyl,
- or heterocyclyl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₄ alkyl,
- C₁-C₄ alkyl substituted by hydroxy,
- C₁-C₄ alkyl substituted by carbocyclic aryl,
- methoxy,
- C₁-C₂ alkoxy carbonyl,
- carbocyclic arylthio substituted by methoxycarbonyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
- halogen,
- halogenated methyl,
- heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula Va, VIIIa, or IXa;

wherein R₄ and R₅ are independently selected from H or C₁-C₃ alkyl;

Y is -(CH₂)_m, m is 0 or 1;

wherein carbocyclic aryl is phenyl, naphthyl, phenanthryl, or biphenyl;

carbocyclyl is 9H-fluorenyl, acenaphthyl, or anthraquinonyl;

heterocyclyl is 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,2-dihydro-3-oxo-pyrazolyl, 1,3-dioxolanyl, 1H-indolyl, 1H-pyrrolyl, 2,2',5',2"-terthiophenyl, 2,2'-bithiophenyl, 2,3-

dihydro-benzo[1,4]dioxinyl, 3,4-dihydro-2*H*-benzo[1,4]oxazinyl, 4-oxo-benzopyranyl, 9*H*-carbazolyl, 9*H*-xanthenyl, benzimidazolyl, benzo[1,3]dioxolyl, benzo[*b*]thienyl, benzofuryl, benzothiazolyl, furyl, imidazolyl, isoxazolyl, oxolanyl, pyrazolo[5,1-*b*]thiazolyl, pyrazolyl, pyridyl, pyrimidyl, quinolyl, quinoxalyl, thiazolidyl, thiazolyl, thienyl, 2*H*-benzopyranyl, 4*H*-benzo[1,3]dioxinyl, azetidyl, imidazo[2,1-*b*]thiazolyl, morpholinyl, or 2,3-dihydro-benzofuryl;

halogen is fluoro, chloro, bromo, or iodo.

Other more preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₇ alkyl substituted by substituent(s) independently selected from

- methoxy,
- methoxy substituted by carbocyclic aryl,
- carbocyclic aryloxy,
- halogenated carbocyclic aryloxy,
- mono-ethylamino substituted by cyano,
- di-methylamino substituted by carbocyclic aryl,
- mono-carbocyclic arylamino,
- mono-carbocyclic arylamino substituted by methyl,
- carbocyclic arylsulfonylamino substituted by methyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - nitro,
 - C₁-C₄ alkyl,
 - C₁-C₄ alkyl substituted by carbocyclic aryl,
 - C₁-C₄ alkyl substituted by hydroxy,
 - methoxy,
 - halogenated methoxy,
 - heterocyclyl substituted by carbocyclic aryl,

(ii) C₂-C₇ alkenyl substituted by substituent(s) independently selected from

- methoxy substituted by carbocyclic aryl,
- carbocyclic aryl,
- carbocyclic aryl substituted by methoxy,

(iii) butynyl substituted by carbocyclic aryl,

(iv) cyclohexyl substituted by carbocyclic arylmethyl,

(v) carbocyclyl,

(vi) carbocyclic aryl,

carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,
- hydroxy,
- cyano,
- amino,
- C₁-C₂ alkyl,
- halogenated methyl,
- C₁-C₃ alkoxy,
- C₁-C₃ alkoxy substituted by substituent(s) independently selected from
 - halogen,
 - halogenated carbocyclic aryl,
- propenyloxy,
- di-C₁-C₂ alkylamino,
- di-C₁-C₂ alkylamino substituted by cyano,
- methylthio,
- halogenated methylthio,

(vii) heterocyclyl,

or heterocyclyl substituted by substituent(s) independently selected from

- halogen,
- C₁-C₃ alkyl,
- C₁-C₃ alkyl substituted by hydroxy,
- C₁-C₃ alkyl substituted by carbocyclic aryl,
- methoxy,
- ethoxycarbonyl,

- carbocyclic arylthio substituted by methoxycarbonyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - halogenated methyl,
- heterocyclyl;

R₂ is methylamino or dimethylamino;

L is selected from Formula XX - XXII;

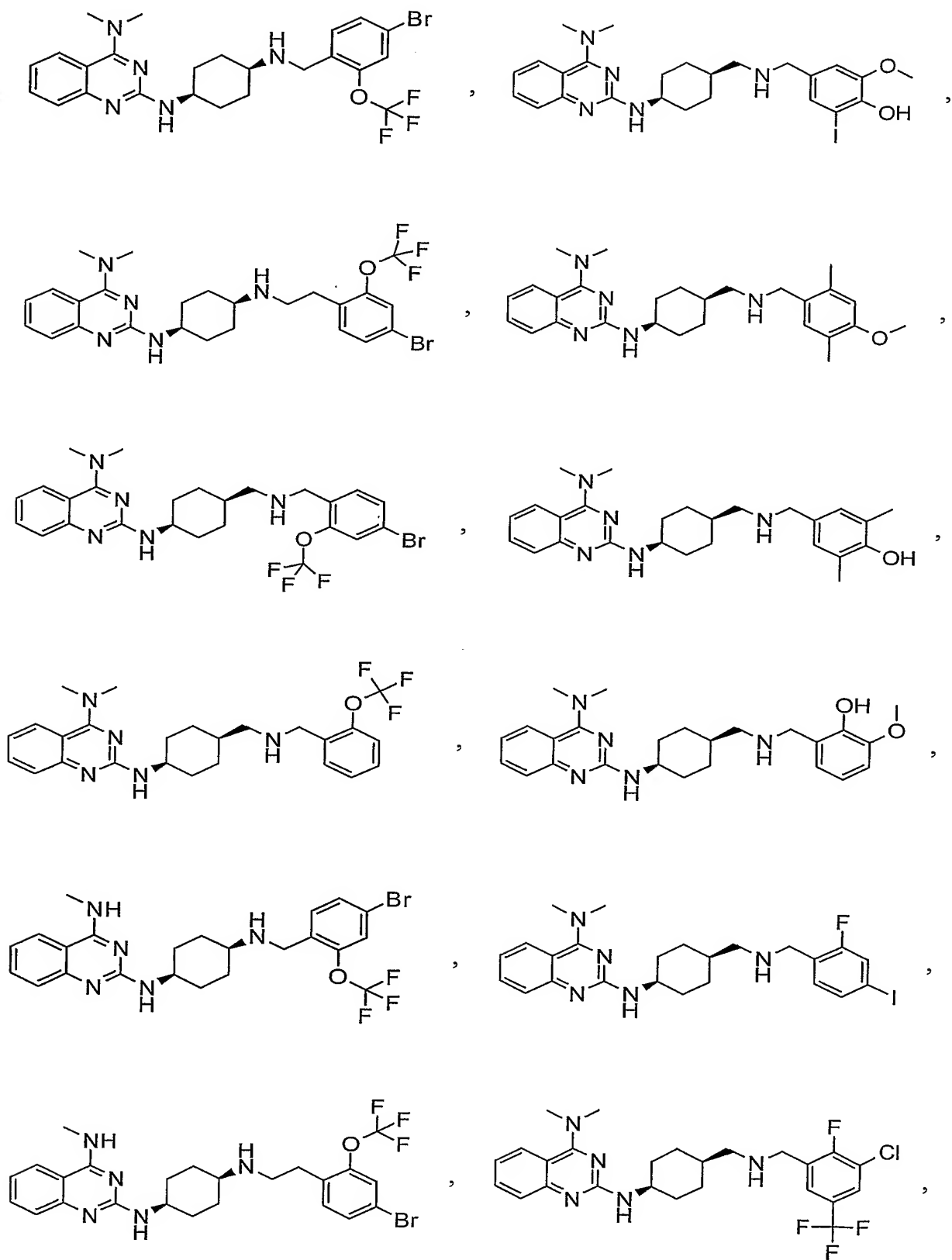
Y is -(CH₂)_m, m is 0 or 1;

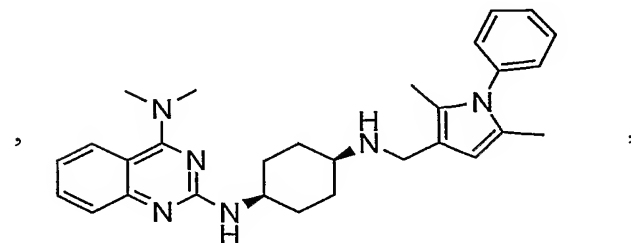
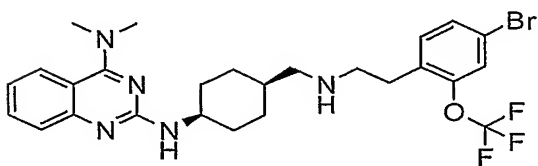
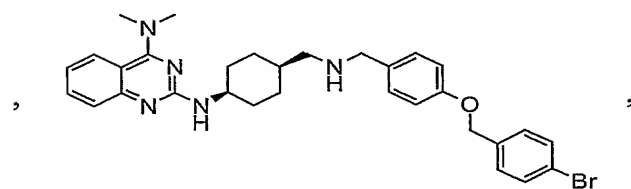
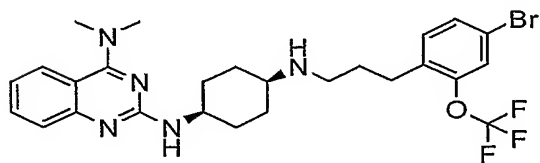
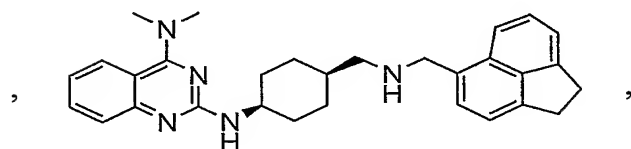
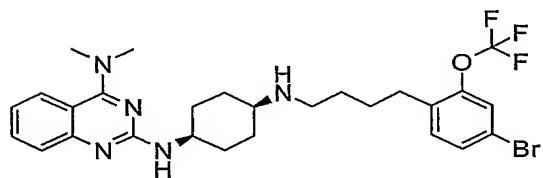
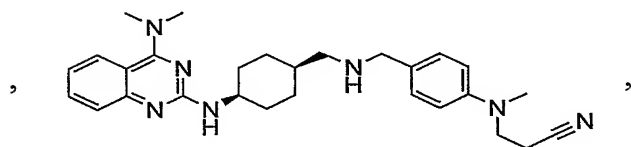
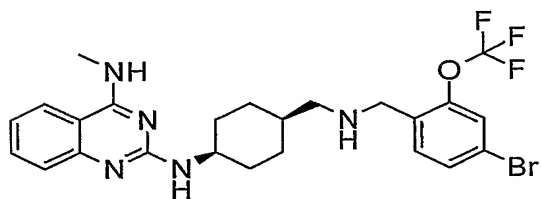
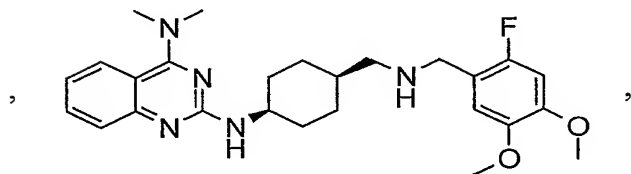
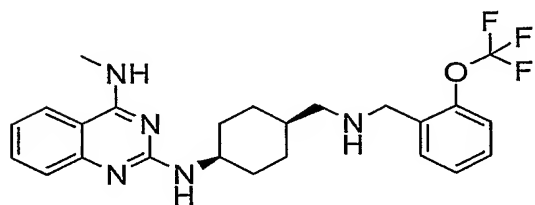
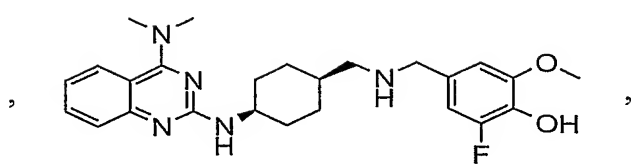
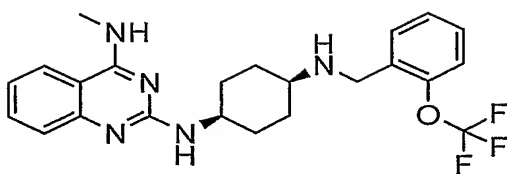
wherein carbocyclic aryl is phenyl, **naphthyl**, or biphenyl;

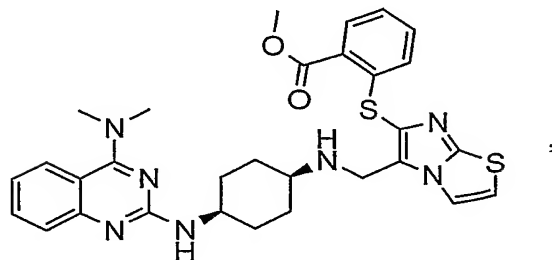
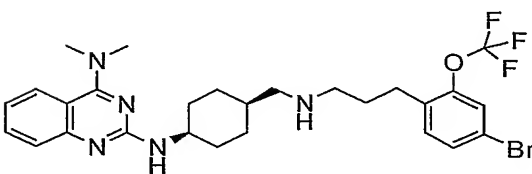
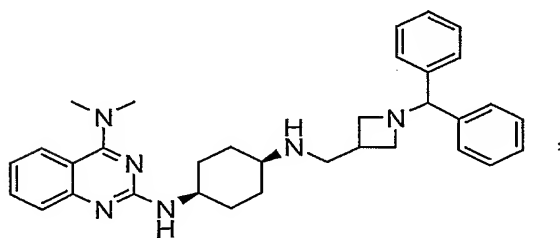
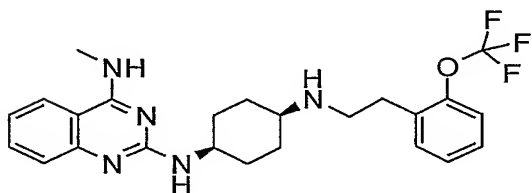
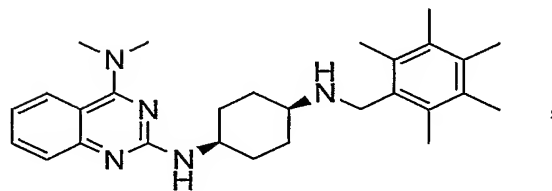
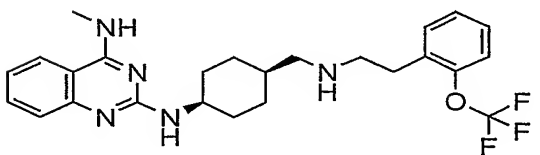
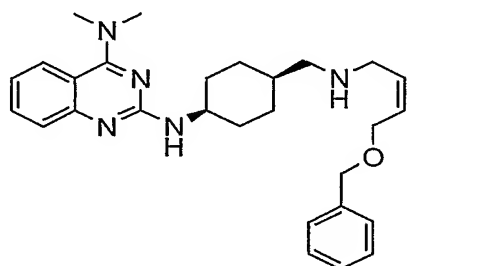
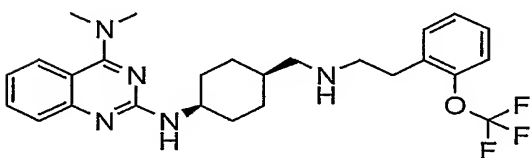
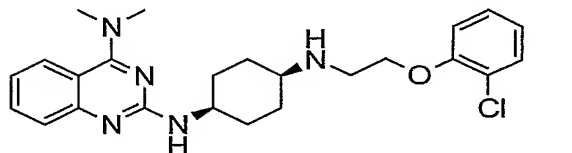
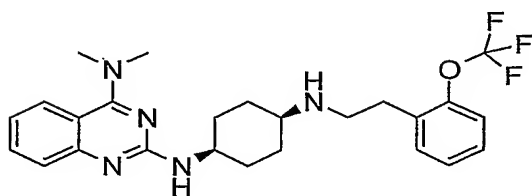
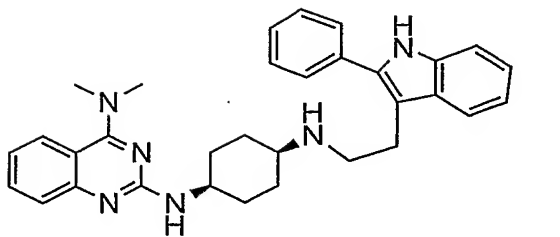
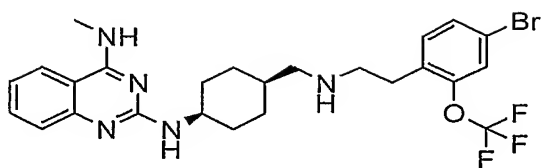
carbocyclyl is acenaphthyl;

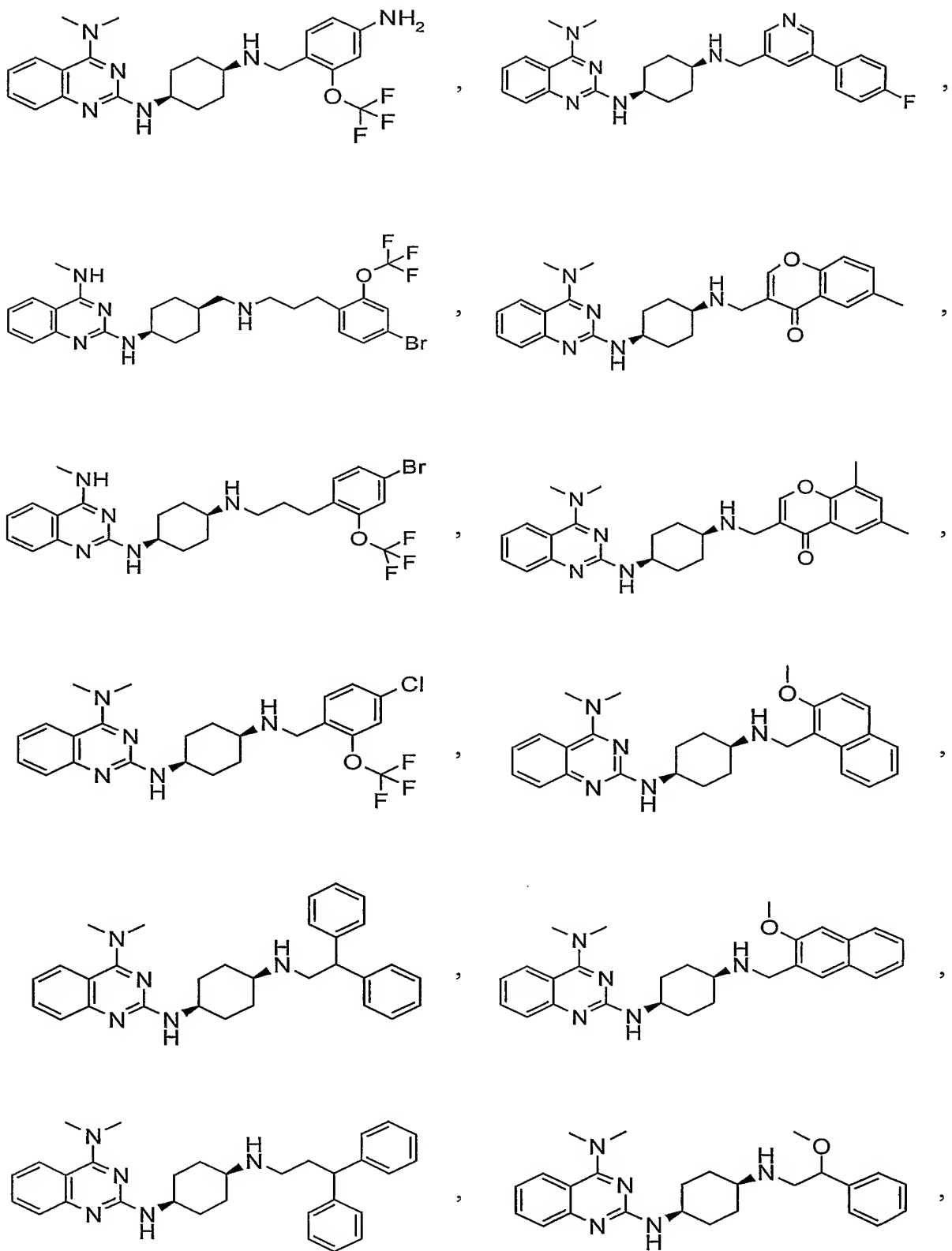
heterocyclyl is 1*H*-indolyl, 1*H*-pyrrolyl, 2,3-dihydro-benzo[1,4]dioxinyl, 9*H*-carbazolyl, benzo[1,3]dioxolyl, furyl, pyrazolyl, thienyl, 4-oxo-benzopyranyl, azetidiny, imidazo[2,1-*b*]thiazolyl, pyridyl, imidazolyl, 2,3-dihydro-benzofuryl, or benzo[*b*]thienyl;;
halogen is fluoro, chloro, bromo, or iodo.

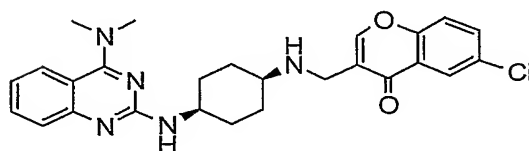
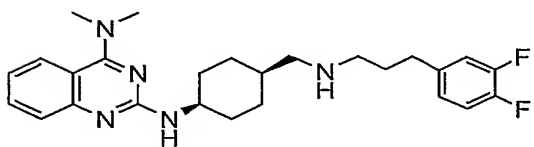
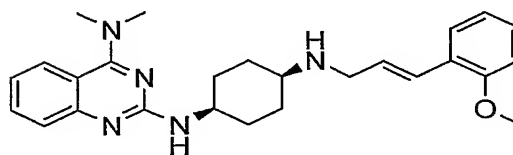
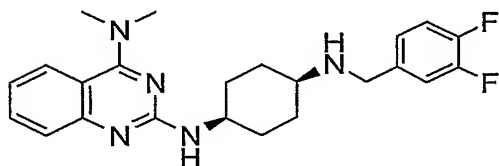
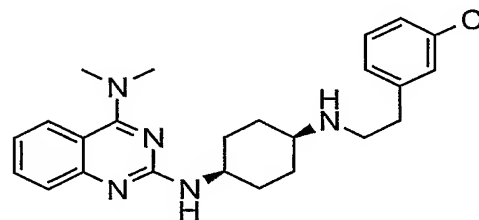
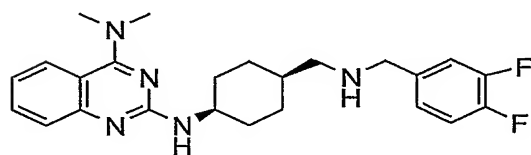
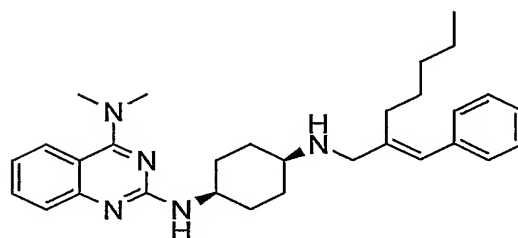
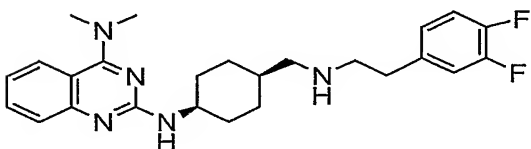
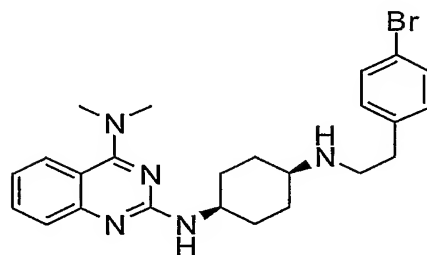
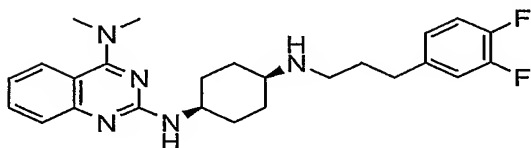
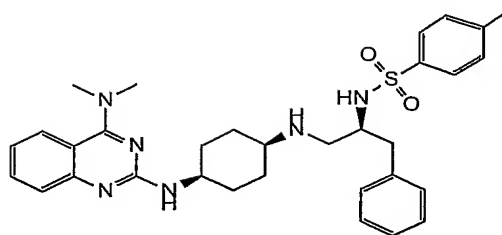
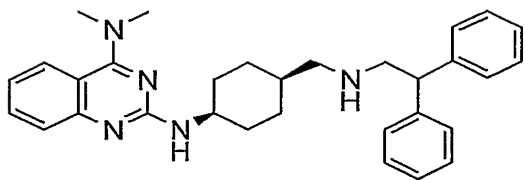
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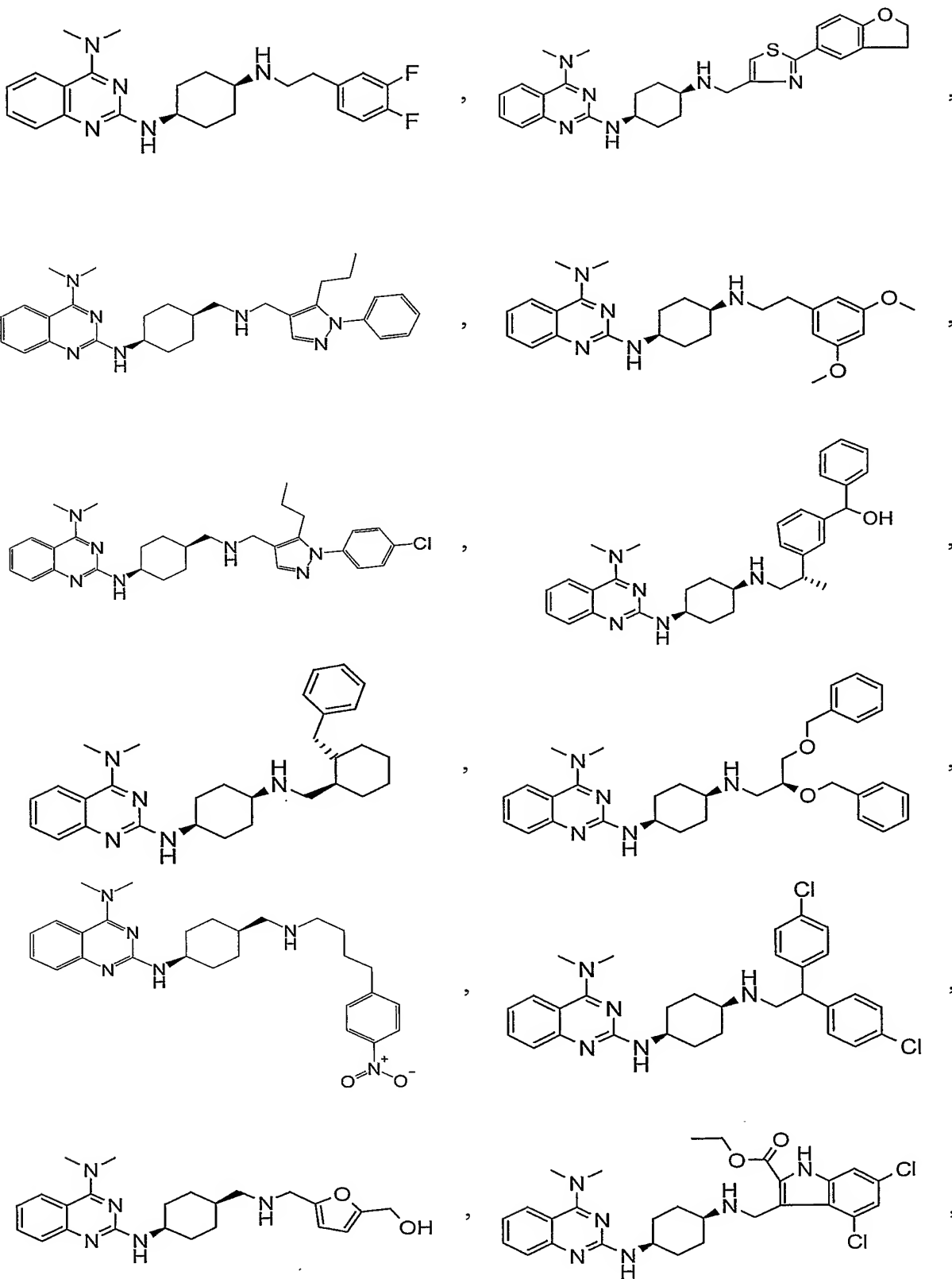


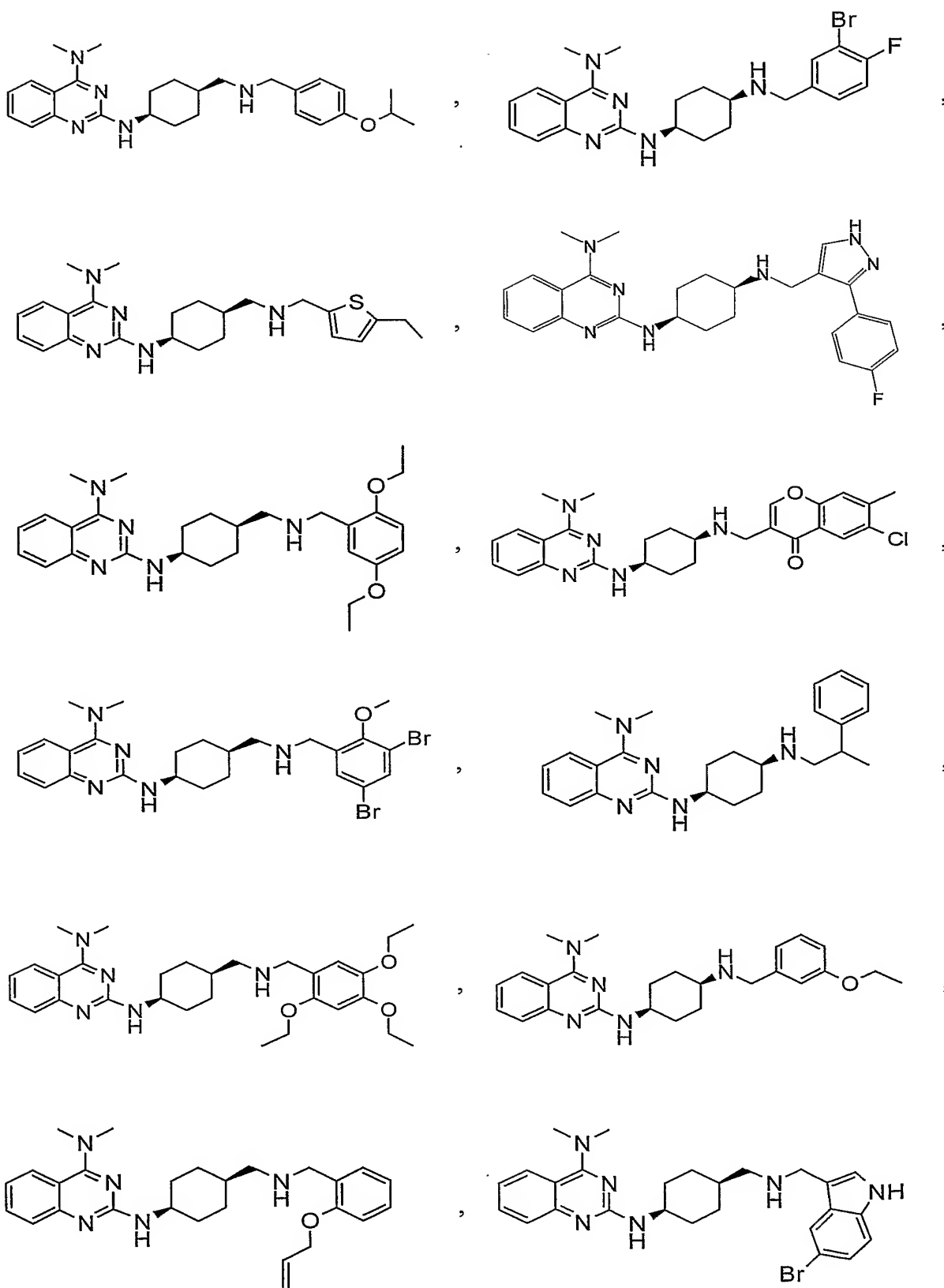


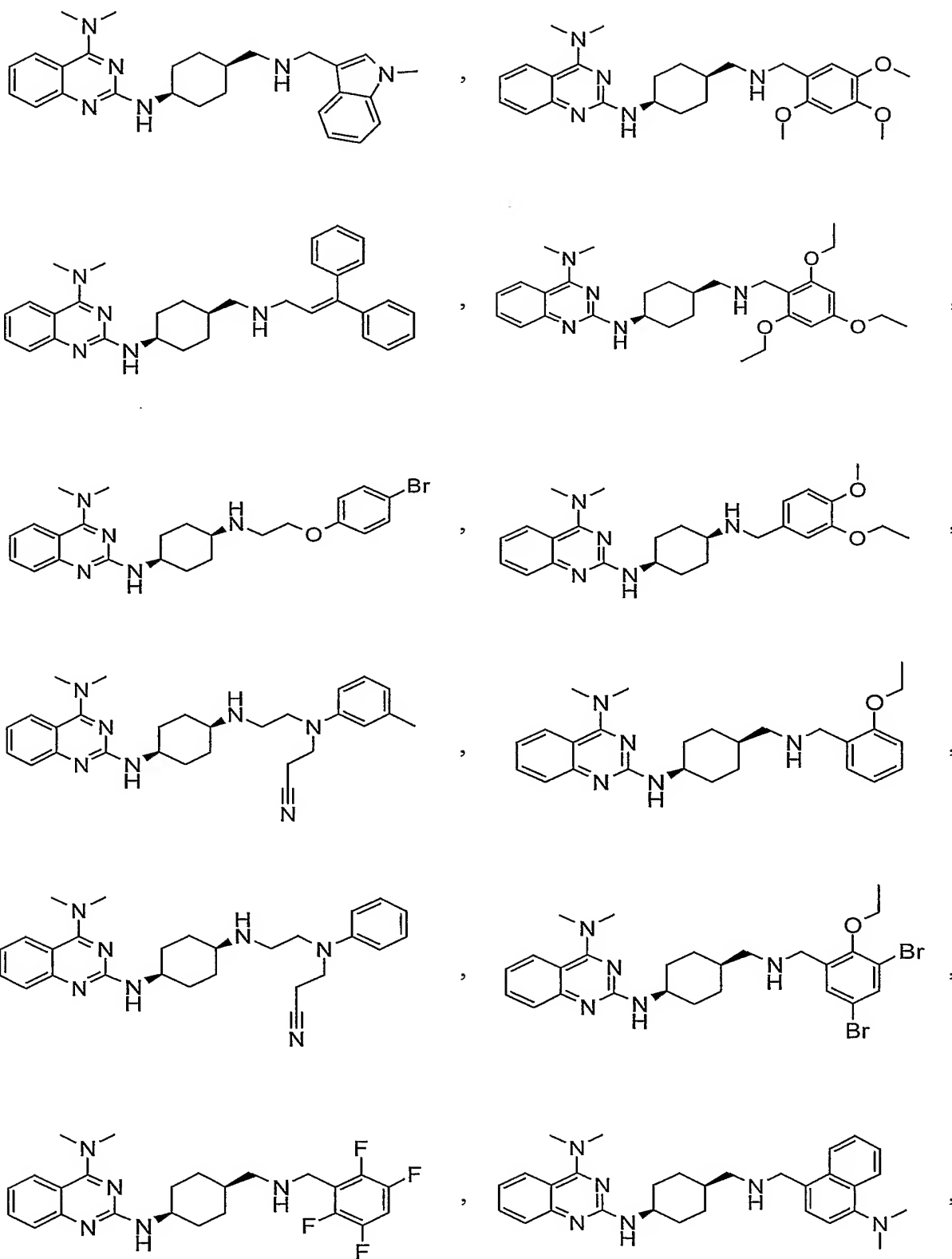


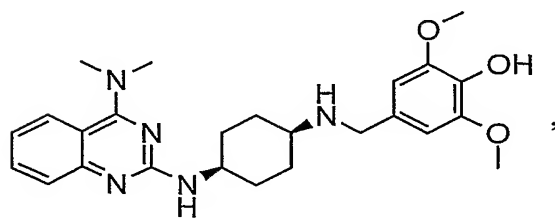
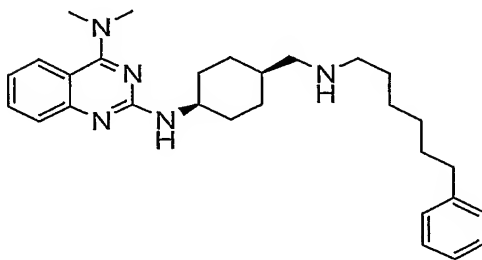
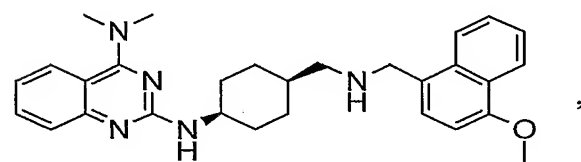
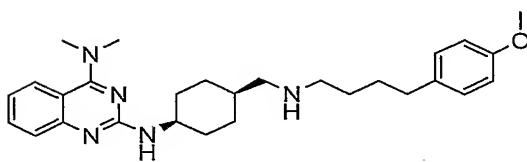
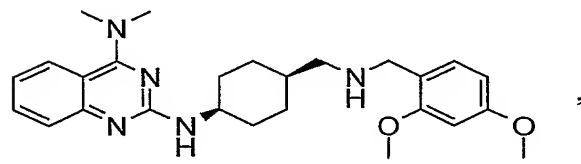
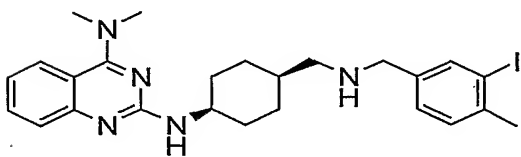
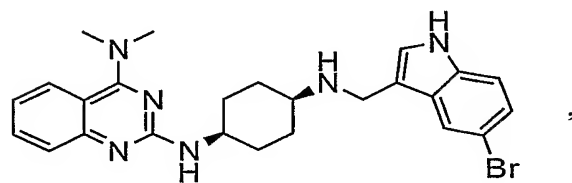
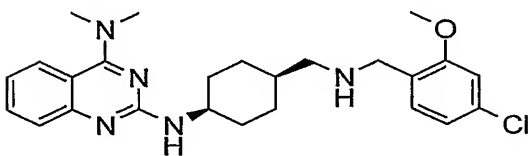
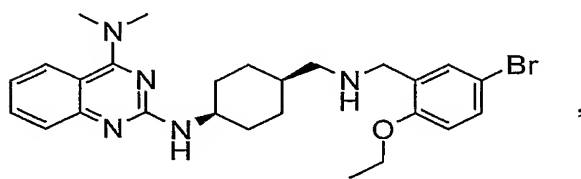
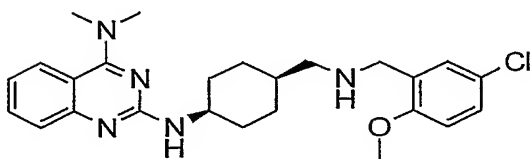
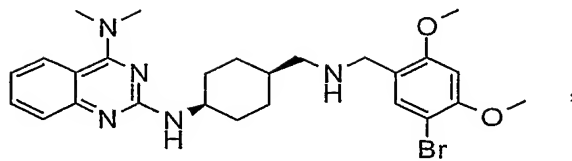
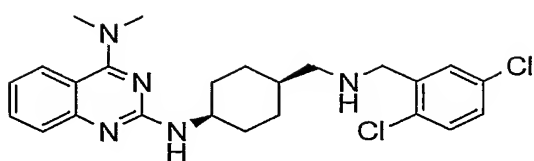


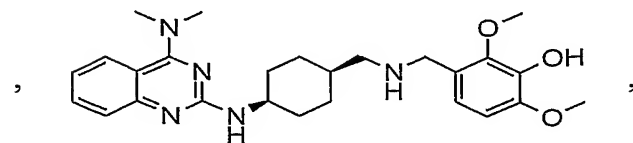
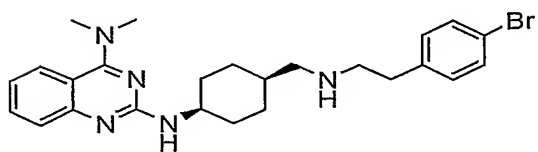
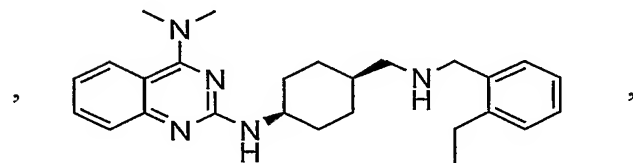
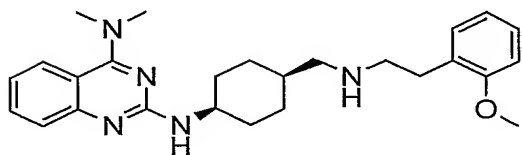
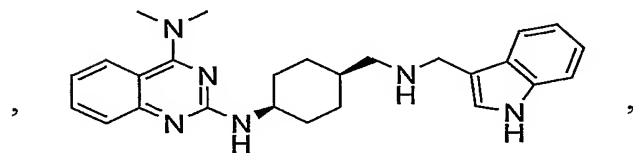
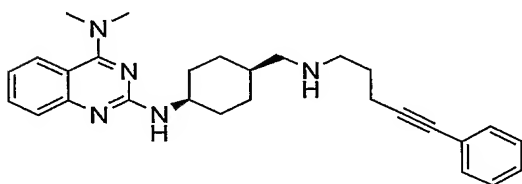
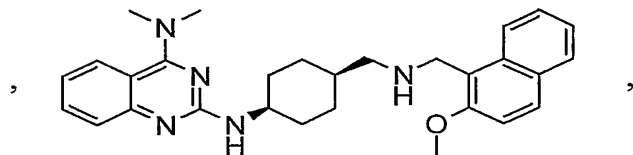
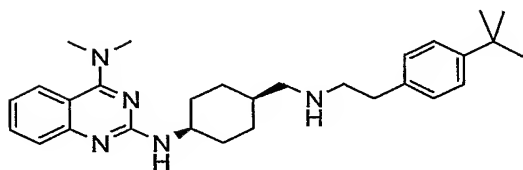
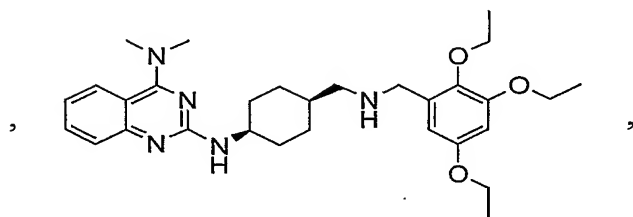
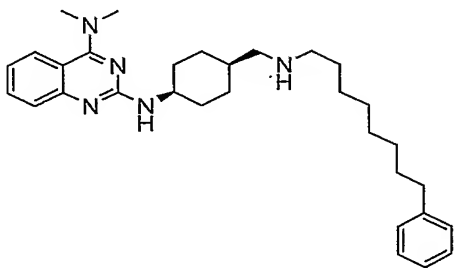
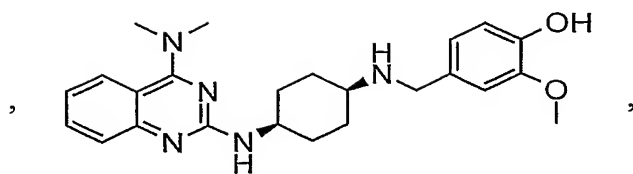
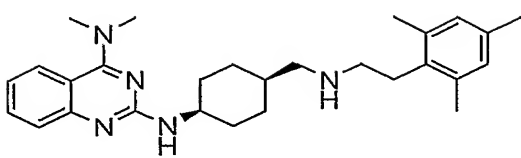


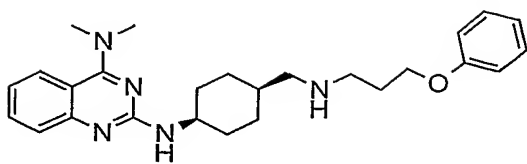




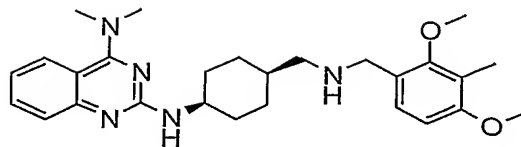




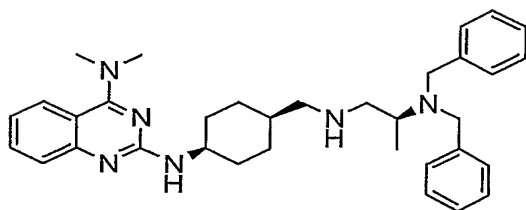




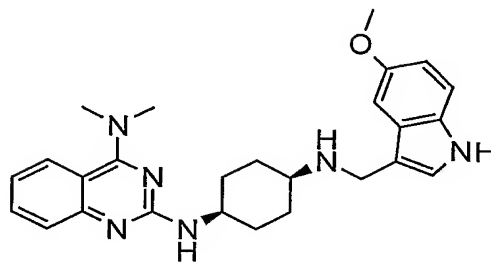
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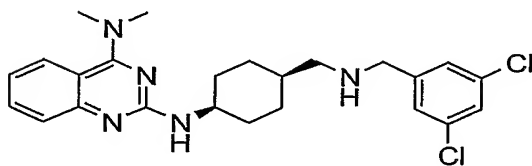
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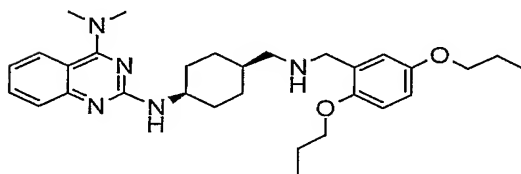
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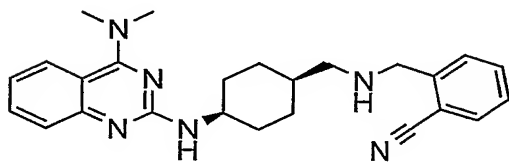
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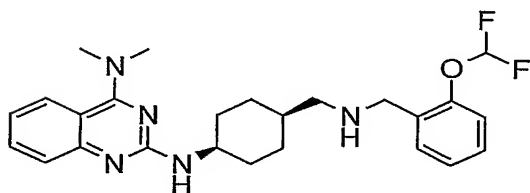
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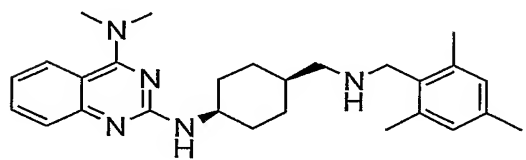
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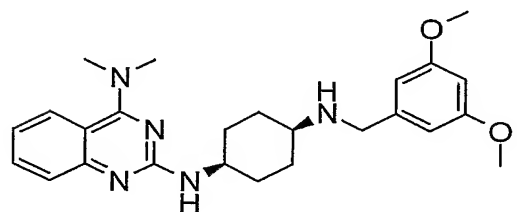
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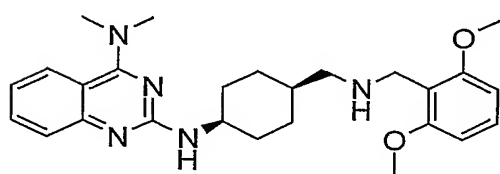
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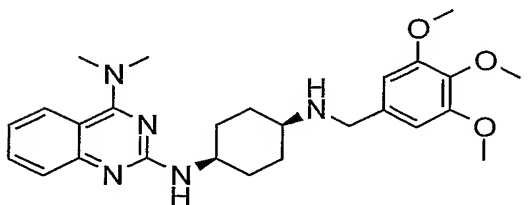
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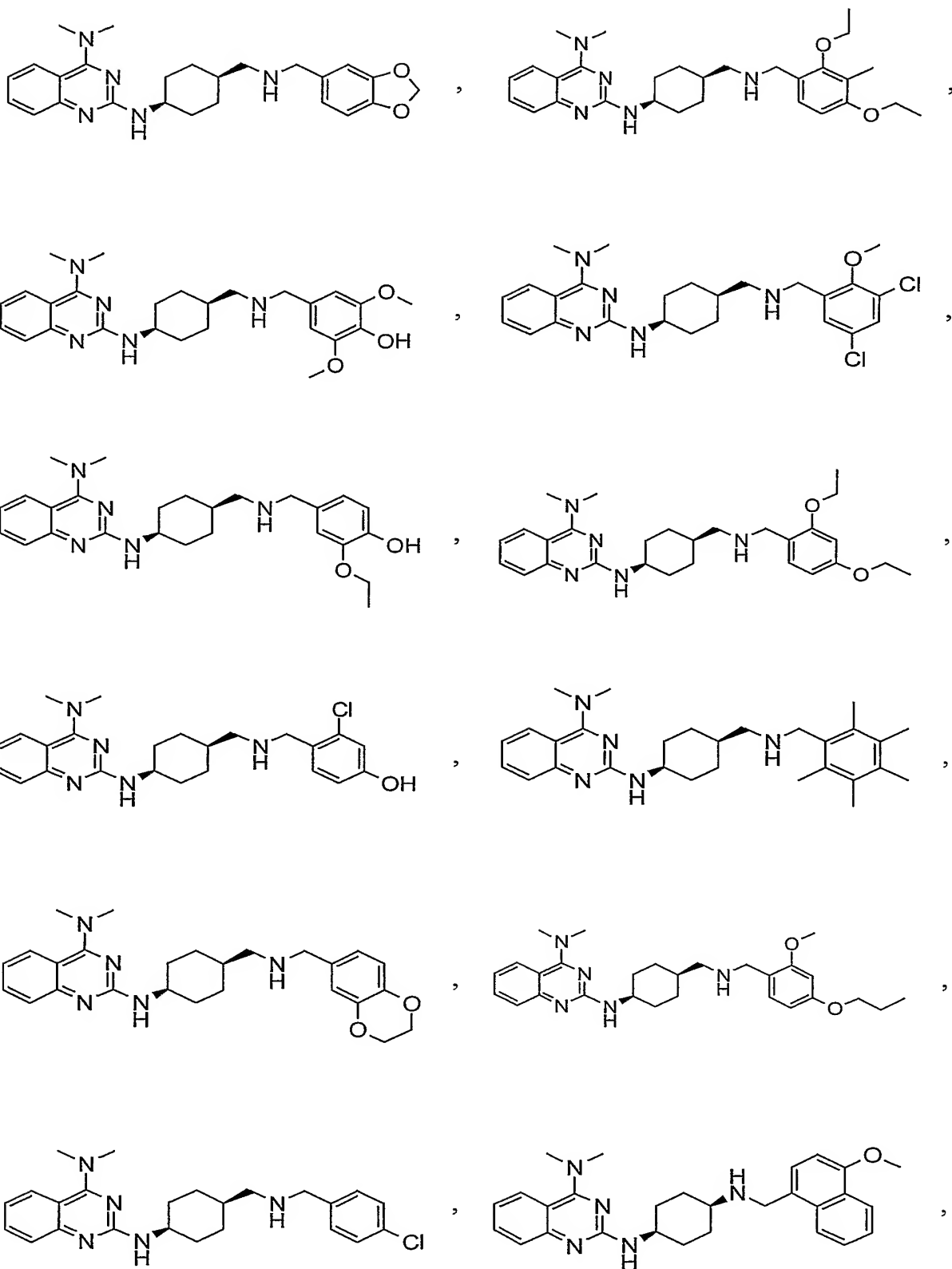
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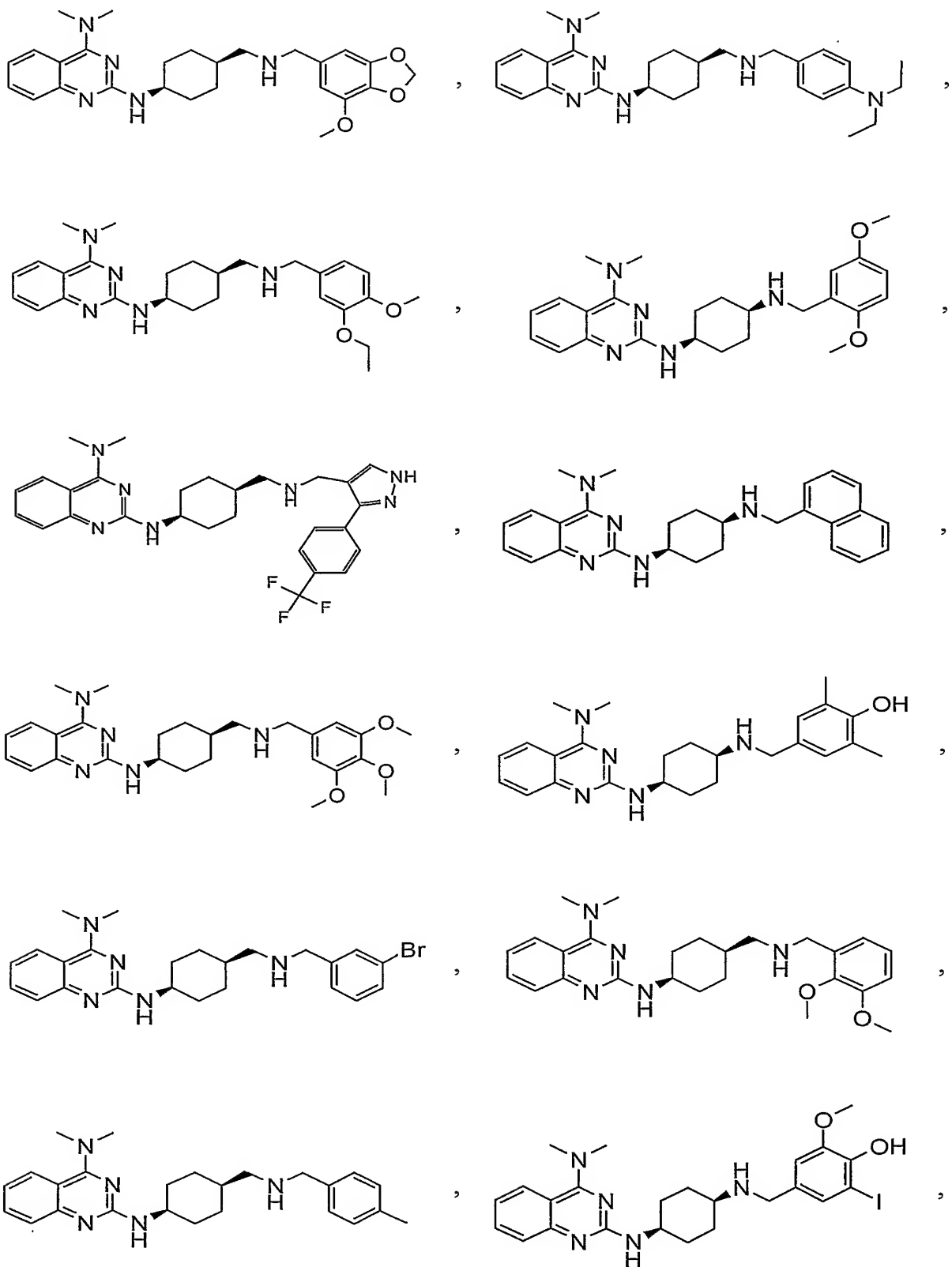


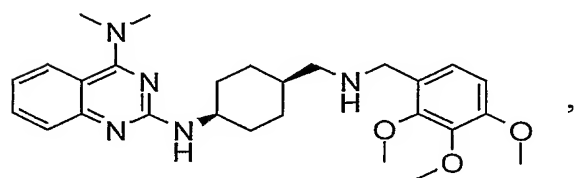
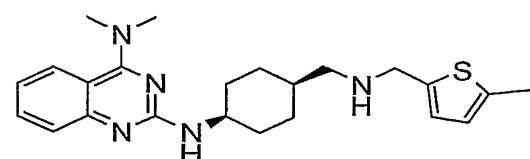
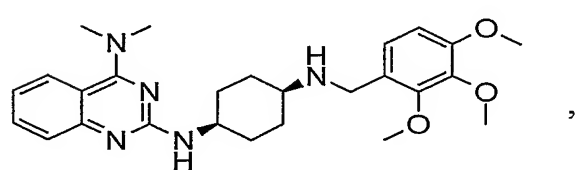
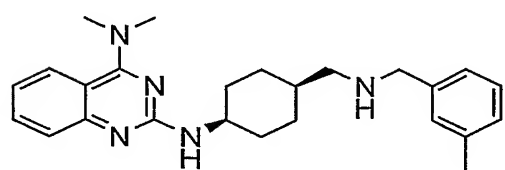
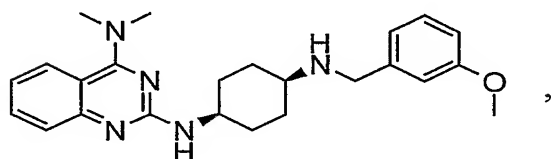
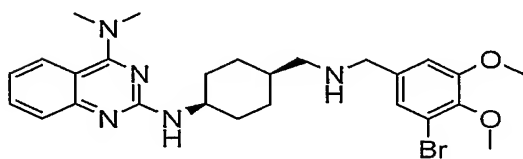
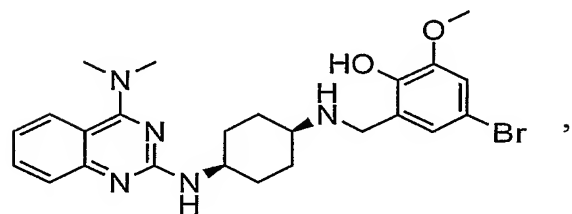
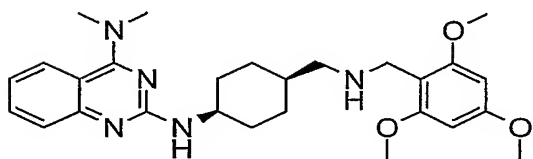
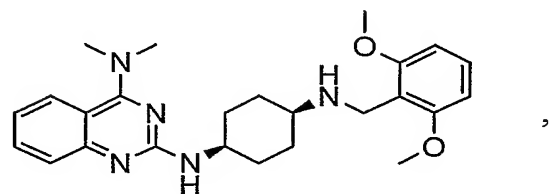
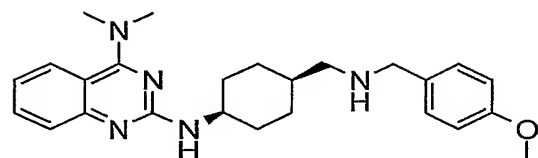
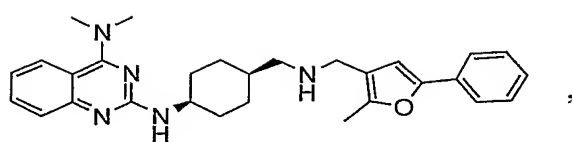
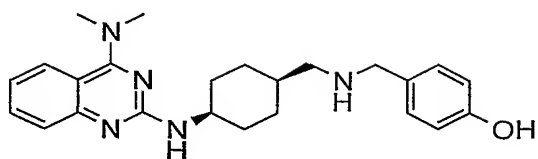
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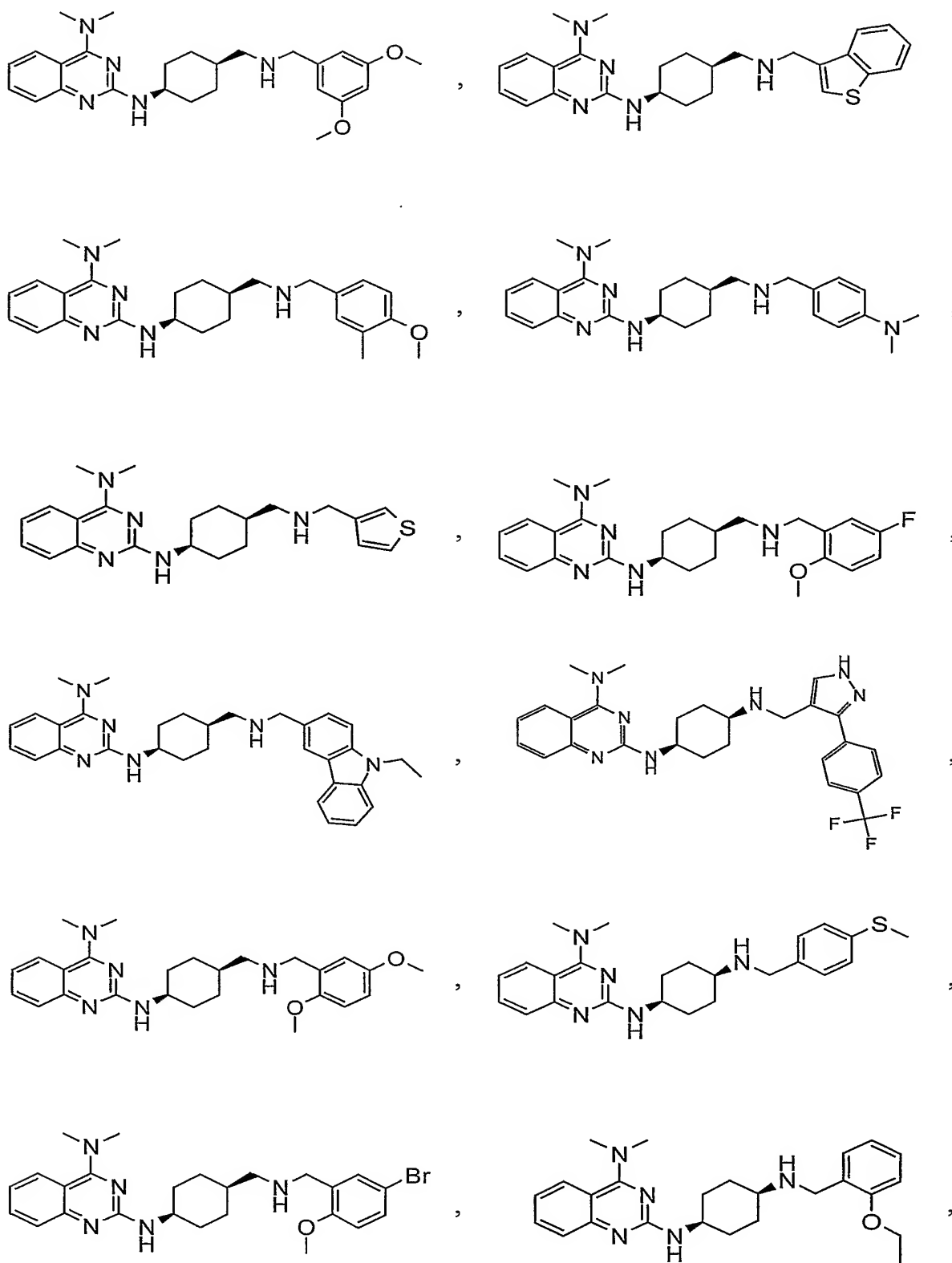


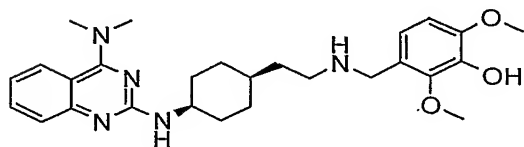
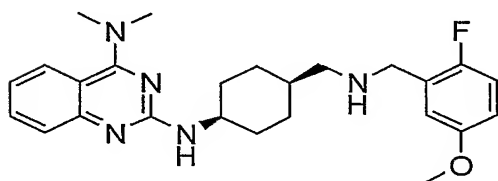
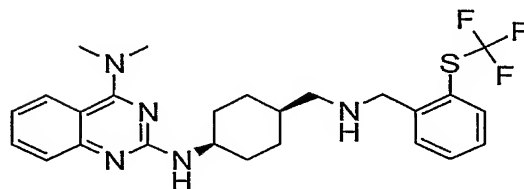
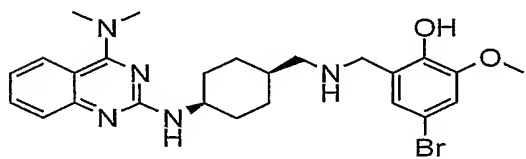
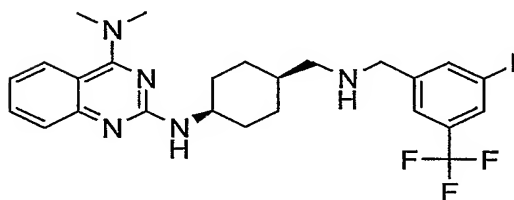
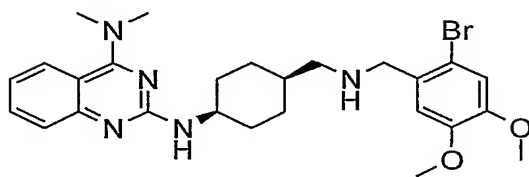
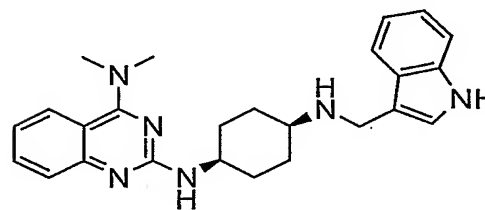
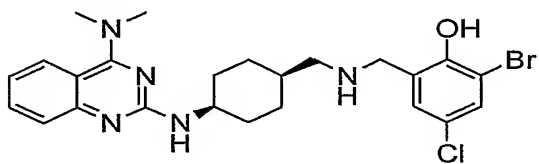
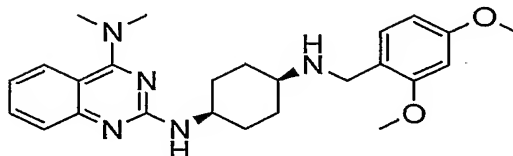
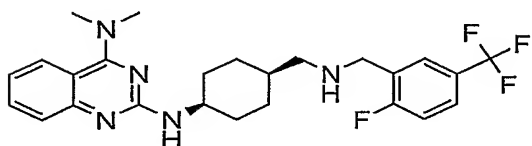
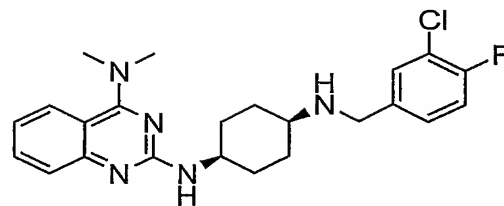
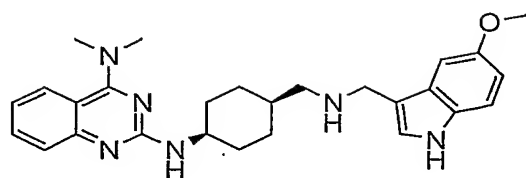
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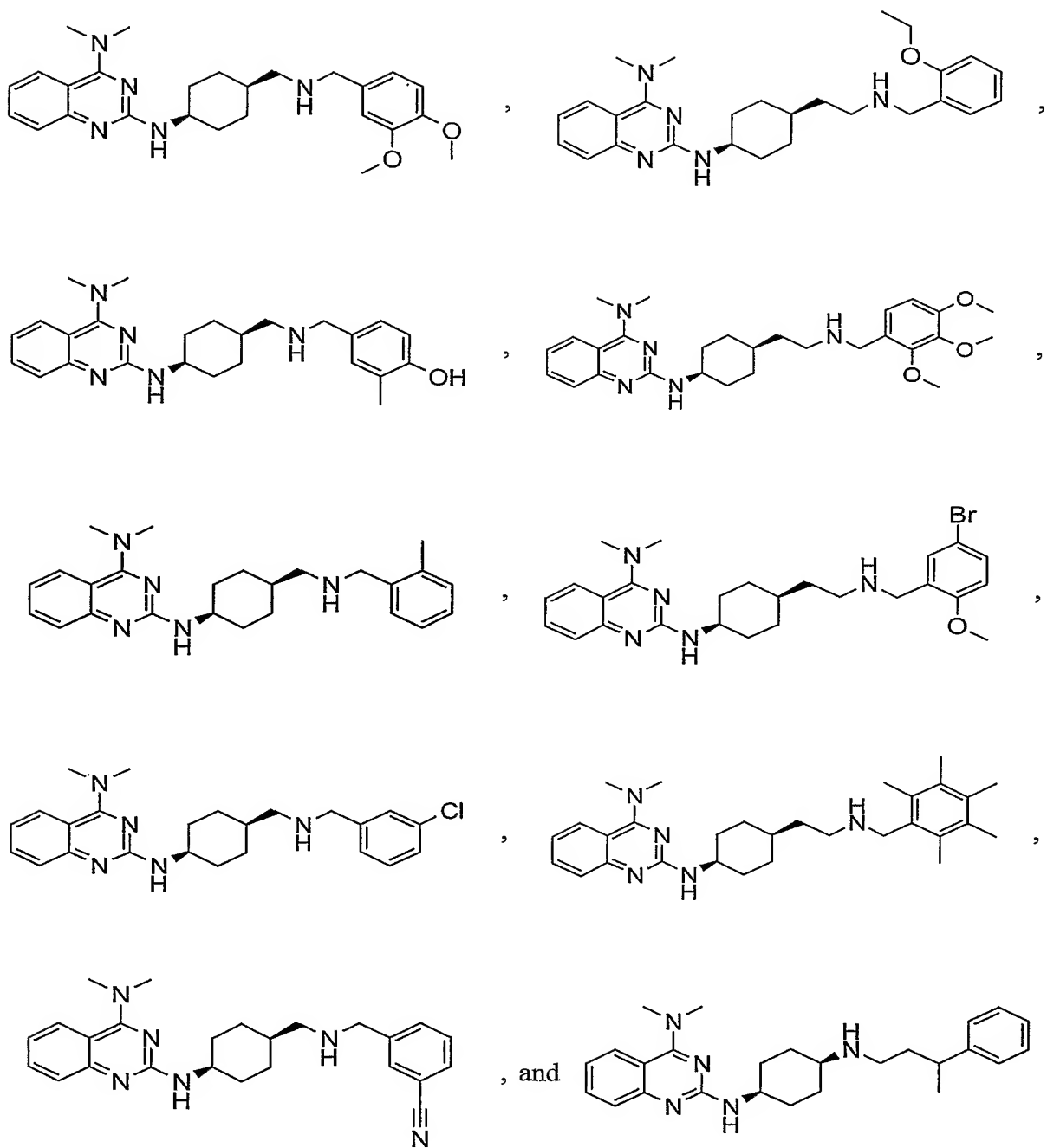












; or, in case of, a salt thereof.

Preferred compounds of this invention are those compounds of Formula I wherein,

Q is Formula II;

R₁ represents

(i) C₁-C₁₆ alkyl,

C₁-C₁₆ alkyl substituted by substituent(s) independently selected from

- halogen,

- carbocyclyl,

- carbocyclic aryl,

- carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,

- nitro,

- C₁-C₃ alkyl,

- halogenated C₁-C₃ alkyl,

(ii) C₂-C₃ alkenyl,

C₂-C₃ alkenyl substituted by carbocyclic aryl,

(iii) carbocyclic aryl,

carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,

- cyano,

- nitro,

- C₁-C₅ alkyl,

- C₁-C₅ alkyl substituted by substituent(s) independently selected from

- halogen,

- oxo,

- C₂-C₃ alkenyl,

- C₁-C₄ alkoxy,

- C₁-C₄ alkoxy substituted by substituent(s) independently selected from

- halogen,

- heterocyclyl,

- halogenated heterocyclyl,

- carbocyclic aryloxy,

- carbocyclic aryloxy substituted by substituent(s) independently selected from

- halogen,
- nitro,
- heterocycloxy,
- heterocycloxy substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- C₁-C₃ alkoxycarbonyl,
- mono- or di-C₁-C₄ alkylamino,
- C₁-C₃ alkylcarbonylamino,
- carbocyclic aryl diazo,
- carbocyclic aryl diazo substituted by mono- or di- C₁-C₃ alkylamino,
- C₁-C₃ alkylsulfonyl,
- carbocyclic aryl,
- (iv) heterocyclyl,
- or heterocyclyl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- C₁-C₃ alkyl substituted by substituent(s) independently selected from
- halogen,
- oxo,
- carbocyclic arylcarbonylamino,
- halogenated carbocyclic arylcarbonylamino,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
- halogen,
- C₁-C₃ alkyl,
- halogenated C₁-C₃ alkyl,
- C₁-C₃ alkoxy,
- C₁-C₃ alkylcarbonylamino,
- carbocyclic arylsulfonyl,
- C₁-C₃ alkoxycarbonyl,

- carbocyclic aryl,
- halogenated carbocyclic aryl,
- heterocyclyl,
- heterocyclyl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - halogenated C₁-C₃ alkyl;

R₂ is -NHNH₂, -NHNHBoc, -N(R_{2a})(R_{2b}); morpholino, 4-acetyl-piperazyl, or 4-phenyl-piperazyl;

wherein R_{2a} is H or C₁-C₃ alkyl;

R_{2b} is C₁-C₄ alkyl, C₁-C₄ alkyl substituted by substituent(s) independently selected from

- hydroxy,
- C₁-C₃ alkoxy,
- amino,
- NHBoc,
- C₃-C₆ cycloalkyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from
 - halogen,
 - C₁-C₃ alkyl,
 - C₁-C₃ alkoxy,
 - SO₂NH₂,
 - heterocyclyl,

C₃-C₆ cycloalkyl, carbocyclic aryl, carbocyclic aryl substituted by substituent(s) independently selected from

- halogen,
- C₁-C₃ alkyl,
- C₁-C₃ alkoxy,

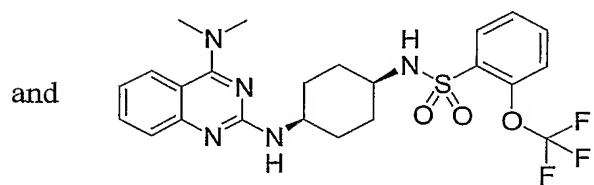
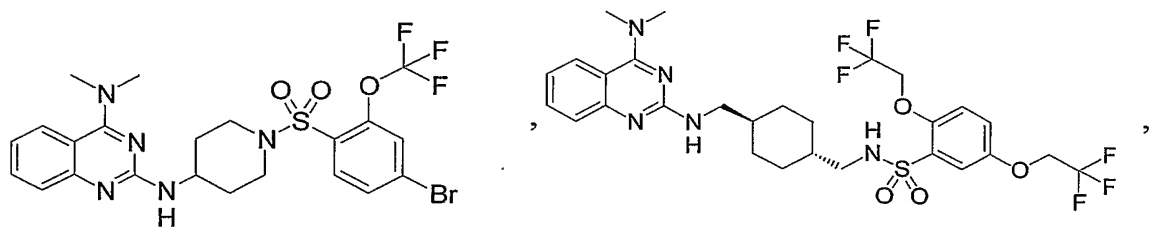
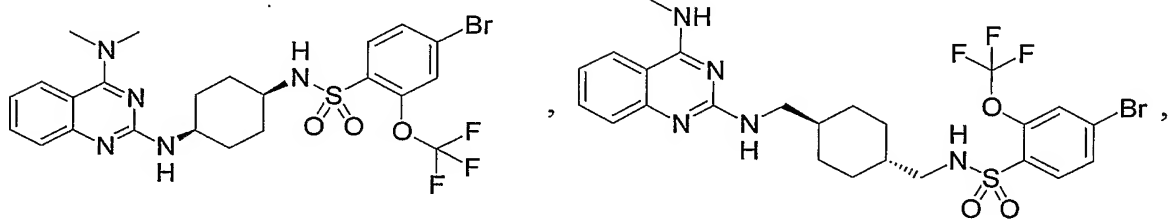
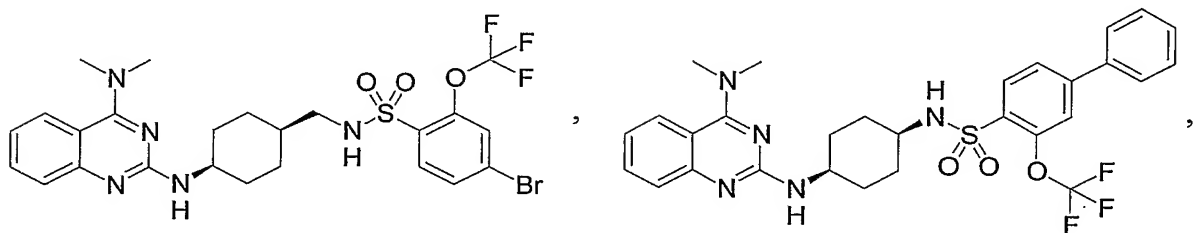
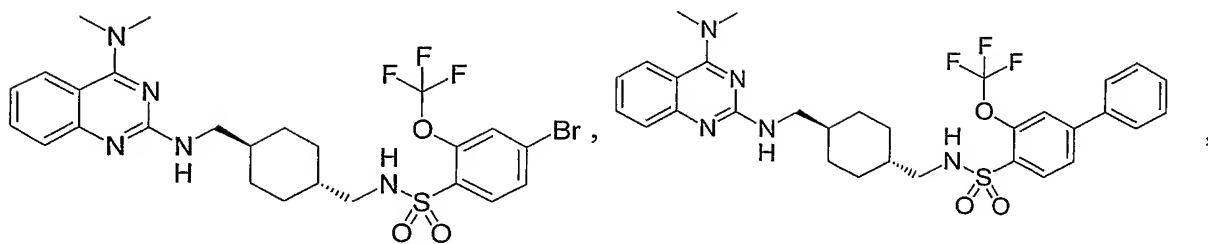
or a group of Formula IV;

wherein Boc is carbamic acid *tert*-butyl ester and R₃ is C₁-C₃ alkyl or C₁-C₃ alkyl substituted by substituent(s) independently selected from

- carbocyclic aryl,

- halogenated carbocyclic aryl,
- carbocyclic aryl substituted by C₁-C₃ alkoxy;
 - L is selected from Formula V - XIX;
 - wherein R₄ is H or C₁-C₃ alkyl;
 - R₅ is H, C₁-C₃ alkyl, or C₁-C₃ alkyl substituted by a substituted carbocyclic aryl;
 - Y is -S(O)₂-;
 - wherein carbocyclic aryl is phenyl, naphthyl, or biphenyl;
 - carbocyclyl is 7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptyl;
 - heterocyclyl is 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3-thiadiazolyl, 1*H*-pyrrolyl, benzo[2,1,3]oxadiazolyl, benzo[b]thienyl, furyl, imidazolyl, isoxazolyl, pyrazolyl, pyridyl, quinolyl, thiazolyl, or thienyl;
 - halogen is fluoro, chloro, bromo, or iodo.

The following compounds are specially preferred;



; or, in case of, a salt thereof.

Preferred compounds of this invention are those compounds of Formula I wherein,
Q is Formula II;
R₁ is selected from H, -CO₂^tBu, or -CO₂Bn (Bn is a benzyl group);
R₂ is methylamino or dimethylamino;
L is selected from Formula XX - XXII;
Y is a single bond;
or a salt thereof.

One embodiment of the invention includes any compound of the invention which selectively binds an MCH receptor, such selective binding is preferably demonstrated by a K_i for one or more other GPCR(s), preferably NPY, being at least 10-fold greater than the K_i for any particular MCH receptor, preferable MCHR1.

As used herein, the term "alkyl" is intended to denote hydrocarbon compounds including straight chain and branched chain, including for example but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, tert-pentyl, n-hexyl, and the like.

The term "alkoxy" is intended to denote substituents of the formula
-O-alkyl.

At various places in the present specification substituents of compounds of the invention are disclosed in groups. It is specifically intended that the invention include each and every individual subcombination of the members of such groups.

G-protein coupled receptors (GPCRs) represent a major class of cell surface receptors with which many neurotransmitters interact to mediate their effects. GPCRs are predicted to have seven membrane-spanning domains and are coupled to their effectors via G-proteins linking receptor activation with intracellular biochemical sequelae such as stimulation of adenylyl cyclase. Melanin Concentrating Hormone (MCH), a cyclic peptide, has been identified as the endogenous ligand of the orphan G-protein coupled receptor SLC-1. See, for example, Shimomura et al., *Biochem. Biophys. Res. Commun.* 261, 622-26 (1999). Studies have indicated that MCH acts as a neurotransmitter/modulator/regulator to alter a number of behavioral responses.

Mammalian MCH (19 amino acids) is highly conserved between rat, mouse, and human, exhibiting 100% amino acid identity, but its physiological roles are less clear. MCH

has been reported to participate in a variety of processes including feeding, water balance, energy metabolism, general arousal/attention state, memory and cognitive functions, and psychiatric disorders. For reviews, see 1. Baker, *Int. Rev. Cytol.* 126:1-47 (1991); 2. Baker, *TEM* 5:120-126 (1994); 3. Nahon, *Critical Rev. in Neurobiol* 221:221-262, (1994); 4. Knigge et al., *Peptides* 18(7):1095-1097, (1996). The role of MCH in feeding or body weight regulation is supported by Qu et al., *Nature* 380:243-247, (1996), demonstrating that MCH is over expressed in the hypothalamus of ob/ob mice compared with ob/+mice, and that fasting further increased MCH mRNA in both obese and normal mice during fasting. MCH also stimulated feeding in normal rats when injected into the lateral ventricles as reported by Rossi et al., *Endocrinology* 138:351-355, (1997). MCH also has been reported to functionally antagonize the behavioral effects of α -MSH; see: Miller et al., *Peptides* 14:1-10, (1993); Gonzalez et al, *Peptides* 17:171-177, (1996); and Sanchez et al., *Peptides* 18:3933-396, (1997). In addition, stress has been shown to increase POMC mRNA levels while decreasing the MCH precursor preproMCH (ppMCH) mRNA levels; Presse et al., *Endocrinology* 131:1241-1250, (1992). Thus MCH may serve as an integrative neuropeptide involved in the reaction to stress, as well as in the regulation of feeding and sexual activity; Baker, *Int. Rev. Cytol.* 126:1-47, (1991); Knigge et al., *Peptides* 17:1063-1073, (1996).

The localization and biological activities of MCH peptide suggest that the modulation of MCH receptor activity may be useful in a number of therapeutic applications. MCH is expressed in the lateral hypothalamus, a brain area implicated in the regulation of thirst and hunger: Grillon et al., *Neuropeptides* 31:131-136, (1997); recently orexins A and B, which are potent orexigenic agents, have been shown to have very similar localization to MCH in the lateral hypothalamus; Sakurai et al., *Cell* 92:573-585 (1998). MCH mRNA levels in this brain region are increased in rats after 24 hours of food-deprivation; Herve and Fellmann, *Neuropeptides* 31:237-242 (1997); after insulin injection, a significant increase in the abundance and staining intensity of MCH immunoreactive perikarya and fibres was observed concurrent with a significant increase in the level of MCH mRNA; Bahjaoui-Bouhaddi et al., *Neuropeptides* 24:251-258, (1994). Consistent with the ability of MCH to stimulate feeding in rats; Rossi et al., *Endocrinology* 138:351-355, (1997); is the observation that MCH mRNA levels are upregulated in the hypothalami of obese ob/ob mice; Qu et al., *Nature* 380:243-247, (1996); and decreased in the hypothalami of rats treated with leptin,

whose food intake and body weight gains are also decreased; Sahu, *Endocrinology* 139:795-798, (1998). MCH appears to act as a functional antagonist of the melanocortin system in its effects on food intake and on hormone secretion within the HPA (hypothalamopituitary/adrenal axis); Ludwig et al., *Am. J. Physiol. Endocrinol. Metab.* 274:E627-E633, (1998). Together these data suggest a role for endogenous MCH in the regulation of energy balance and response to stress, and provide a rationale for the development of specific compounds acting at MCH receptors for use in the treatment of obesity and stress-related disorders.

Accordingly, a MCH receptor antagonist is desirable for the prophylaxis or treatment of obesity or obesity related disorders. An obesity related disorder is a disorder that has been directly or indirectly associated to obesity, such as, type II diabetes, syndrome X, impaired glucose tolerance, dyslipidaemia, hypertension, coronary heart disease and other cardiovascular disorders including atherosclerosis, insulin resistance associated with obesity and psoriasis, for treating diabetic complications and other diseases such as polycystic ovarian syndrome (PCOS), certain renal diseases including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis, end-stage renal diseases and microalbuminuria as well as certain eating disorders.

In species studied to date, a major portion of the neurons of the MCH cell group occupies a rather constant location in those areas of the lateral hypothalamus and subthalamus where they lie and may be a part of some of the so-called "extrapyramidal" motor circuits. These involve substantial striato- and pallidofugal pathways involving the thalamus and cerebral cortex, hypothalamic areas, and reciprocal connections to subthalamic nucleus, substantia nigra, and mid-brain centers; Bittencourt et al., *J. Comp. Neurol.* 319:218-245, (1992). In their location, the MCH cell group may offer a bridge or mechanism for expressing hypothalamic visceral activity with appropriate and coordinated motor activity. Clinically it may be of some value to consider the involvement of this MCH system in movement disorders, such as Parkinson's disease and Huntingdon's Chorea in which extrapyramidal circuits are known to be involved.

Human genetic linkage studies have located authentic hMCH loci on chromosome 12 (12q23-24) and the variant hMCH loci on chromosome 5 (5q12-13) (Pedoutour et al., 1994). Locus 12q23-24 coincides with a locus to which autosomal dominant cerebellar ataxia type II (SCA2) has been mapped; Auburger et al., *Cytogenet. Cell. Genet.* 61:252-256,

(1992); Twells et al., *Cytogenet. Cell. Genet.* 61:262-265, (1992). This disease comprises neurodegenerative disorders, including an olivopontocerebellar atrophy. Furthermore, the gene for Darier's disease, has been mapped to locus 12q23-24; Craddock et al., *Hum. Mol. Genet.* 2:1941-1943, (1993). Darier's disease is characterized by abnormalities in keratinocyte adhesion and mental illnesses in some families. In view of the functional and neuroanatomical patterns of the MCH neural system in the rat and human brains, the MCH gene may represent a good candidate for SCA2 or Darier's disease. Interestingly, diseases with high social impact have been mapped to this locus. Indeed, the gene responsible for chronic or acute forms of spinal muscular atrophies has been assigned to chromosome 5q12-13 using genetic linkage analysis; Melki et al., *Nature (London)* 344:767-768, (1990); Westbrook et al., *Cytogenet. Cell. Genet.* 61:225-231, (1992). Furthermore, independent lines of evidence support the assignment of a major schizophrenia locus to chromosome 5q11.2-13.3; Sherrington et al., *Nature (London)* 336:164-167, (1988); Bassett et al., *Lancet* 1:799-801, (1988); Gilliam et al., *Genomics* 5:940-944, (1989). The above studies suggest that MCH may play a role in neurodegenerative diseases and disorders of emotion.

Additional therapeutic applications for MCH-related compounds are suggested by the observed effects of MCH in other biological systems. For example, MCH may regulate reproductive functions in male and female rats. MCH transcripts and MCH peptide were found within germ cells in testes of adult rats, suggesting that MCH may participate in stem cell renewal and/or differentiation of early spermatocytes; Hervieu et al., *Biology of Reproduction* 54:1161-1172, (1996). MCH injected directly into the medial preoptic area (MPOA) or ventromedial nucleus (VMN) stimulated sexual activity in female rats; Gonzalez et al., *Peptides* 17:171-177, (1996). In ovariectomized rats primed with estradiol, MCH stimulated luteinizing hormone (LH) release while anti-MCH antiserum inhibited LH release; Gonzalez et al., *Neuroendocrinology* 66:254-262, (1997). The zona incerta, which contains a large population of MCH cell bodies, has previously been identified as a regulatory site for the pre-ovulatory LH surge; MacKenzie et al., *Neuroendocrinology* 39:289-295, (1984). MCH has been reported to influence release of pituitary hormones including ACTH and oxytocin. MCH analogues may also be useful in treating epilepsy. In the PTZ seizure model, injection of MCH prior to seizure induction prevented seizure activity in both rats and guinea pigs, suggesting that MCH-containing neurons may participate in the neural circuitry underlying PTZ-induced seizure; Knigge and Wagner,

Peptides 18:1095-1097, (1997). MCH has also been observed to affect behavioral correlates of cognitive functions. MCH treatment hastened extinction of the passive avoidance response in rats; McBride et al., Peptides 15:757-759, (1994); raising the possibility that MCH receptor antagonists may be beneficial for memory storage and/or retention. A possible role for MCH in the modulation or perception of pain is supported by the dense innervation of the periaqueductal grey (PAG) by MCH-positive fibers. Finally, MCH may participate in the regulation of fluid intake. ICV infusion of MCH in conscious sheep produced diuretic, natriuretic, and kaliuretic changes in response to increased plasma volume; Parkes, J. Neuroendocrinol. 8:57-63, (1996). Together with anatomical data reporting the presence of MCH in fluid regulatory areas of the brain, the results indicate that MCH may be an important peptide involved in the central control of fluid homeostasis in mammals.

In a recent citation MCHR1 antagonists surprisingly demonstrated their use as an anti-depressants and/or anti-anxiety agents. MCHR1 antagonists have been reported to show antidepressant and anxiolytic activities in rodent models, such as, social interaction, forced swimming test and ultrasonic vocalization. Therefore, MCHR1 antagonists could be useful to independently treat subjects with depression and/or anxiety. Also, MCHR1 antagonists could be useful to treat subjects that suffer from depression and/or anxiety and obesity.

This invention provides a method of treating an abnormality in a subject wherein the abnormality is alleviated by decreasing the activity of a mammalian MCH1 receptor which comprises administering to the subject an amount of a compound which is a mammalian MCH1 receptor antagonist effective to treat the abnormality. In separate embodiments, the abnormality is a regulation of a steroid or pituitary hormone disorder, an epinephrine release disorder, an anxiety disorder, a gastrointestinal disorder, a cardiovascular disorder, an electrolyte balance disorder, hypertension, diabetes, a respiratory disorder, asthma, a reproductive function disorder, an immune disorder, an endocrine disorder, a musculoskeletal disorder, a neuroendocrine disorder, a cognitive disorder, a memory disorder, a sensory modulation and transmission disorder, a motor coordination disorder, a sensory integration disorder, a motor integration disorder, a dopaminergic function disorder, a sensory transmission disorder, an olfaction disorder, a sympathetic innervation disorder, an affective disorder, a stress-related disorder, a fluid-balance disorder, a seizure disorder,

pain, psychotic behavior, morphine tolerance, opiate addiction or migraine.

Compositions of the invention may conveniently be administered in unit dosage form and may be prepared by any of the methods well known in the pharmaceutical art, for example, as described in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., Easton, PA, 1980).

The compounds of the invention can be employed as the sole active agent in a pharmaceutical or can be used in combination with other active ingredients which could facilitate the therapeutic effect of the compound.

Compounds of the present invention or a solvate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as a MCH receptor antagonists. By the term "active ingredient" is defined in the context of a "pharmaceutical composition" and shall mean a component of a pharmaceutical composition that provides the primary pharmaceutical benefit, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit. The term "pharmaceutical composition" shall mean a composition comprising at one active ingredient and at least one ingredient that is not an active ingredient (for example and not limitation, a filler, dye, or a mechanism for slow release), whereby the composition is amenable to use for a specified, efficacious outcome in a mammal (for example, and not limitation, a human).

Pharmaceutical compositions, including, but not limited to, pharmaceutical compositions, comprising at least one compound of the present invention and/or an acceptable salt or solvate thereof (*e.g.*, a pharmaceutically acceptable salt or solvate) as an active ingredient combined with at least one carrier or excipient (*e.g.*, pharmaceutical carrier or excipient) may be used in the treatment of clinical conditions for which a MCH receptor antagonist is indicated. At least one compound of the present invention may be combined with the carrier in either solid or liquid form in a unit dose formulation. The pharmaceutical carrier must be compatible with the other ingredients in the composition and must be tolerated by the individual recipient. Other physiologically active ingredients may be incorporated into the pharmaceutical composition of the invention if desired, and if such ingredients are compatible with the other ingredients in the composition. Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions, and then, if

necessary, forming the resulting mixture into a desired shape.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tableting lubricants, and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives, and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampoule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

It is noted that when the MCH receptor antagonists are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but in other non-human mammals as well. Indeed, recent advances in the area of animal health-care mandate that consideration be given for the use of MCH receptor antagonists for the treatment of obesity in domestic animals (*e.g.*, cats and dogs), and MCH receptor antagonists in other domestic animals where no disease or disorder is evident (*e.g.*, food-oriented animals such as cows, chickens, fish, etc.). Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with the appropriate base or acid in water, in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, dioxane, or acetonitrile are preferred. For instance, when the compound (I) possesses an acidic functional group, it can form an inorganic salt such as an alkali metal salt (*e.g.*, sodium salt, potassium salt, etc.), an alkaline earth metal salt (*e.g.* calcium salt, magnesium salt, barium salt, etc.), and an ammonium salt. When the compound (I) possesses a basic functional group, it can form an inorganic salt (*e.g.*, hydrochloride, sulfate, phosphate, hydrobromate, etc.) or an organic salt (*e.g.*, acetate, maleate, fumarate, succinate, methanesulfonate, p-toluenesulfonate, citrate, tartrate, etc.).

When a compound of the invention contains optical isomers, stereoisomers, regio isomers, rotational isomers, a single substance and a mixture of them are included as a

compound of the invention. For example, when a chemical formula is represented as showing no stereochemical designation(s), such as Formula IX, then all possible stereoisomer, optical isomers and mixtures thereof are considered within the scope of that formula. Accordingly, Formula XXII, specifically designates the cis relationship between the two amino groups on the cyclohexyl ring and therefore this formula is also fully embraced by Formula IX.

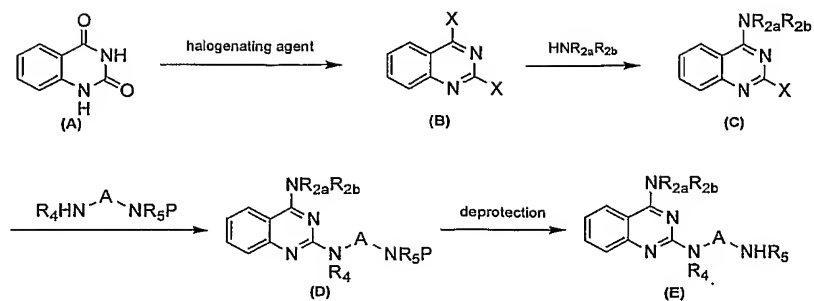
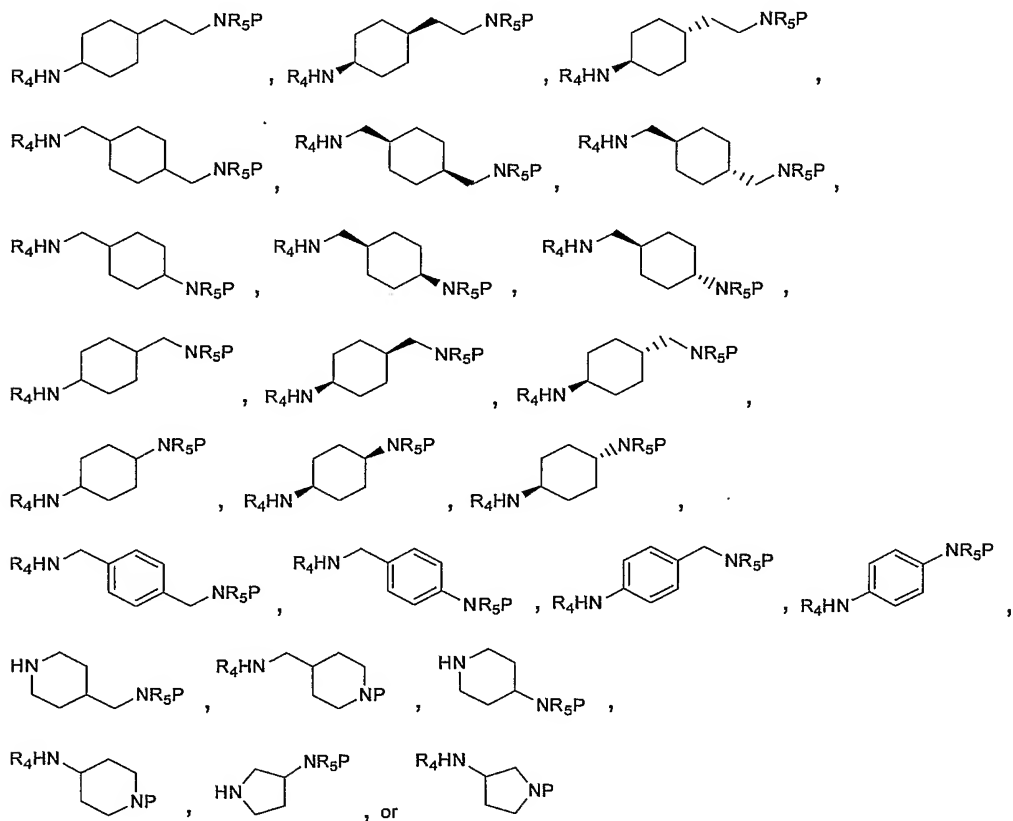
The novel substituted quinazolines of the present invention can be readily prepared according to a variety of synthetic manipulations, all of which would be familiar to one skilled in the art. Preferred methods for the preparation of compounds of the present invention include, but are not limited to, those described in Scheme 1-31.

The common intermediate (E) of the novel substituted quinazolines can be prepared as shown in Scheme 1. Commercially available 1*H*,3*H*-quinazoline-2,4-dione (A) is converted to 2,4-dihalo-quinazoline (B) by a halogenating agent with or without a base (wherein X is halogen such as chloro, bromo, or iodo). The halogenating agent includes phosphorous oxychloride (POCl₃), phosphorous oxybromide (POBr₃), or phosphorus pentachloride (PCl₅). The base includes a tertiary amine (preferably *N,N*-diisopropylethylamine, etc.) or an aromatic amine (preferably *N,N*-dimethylaniline, etc.). Reaction temperature ranges from about 100°C to 200°C, preferably about 140°C to 180°C. The halogen of 4-position of 2,4-dihalo-quinazoline (B) is selectively substituted by a primary or secondary amine (HNR_{2a}R_{2b}, wherein R_{2a} and R_{2b} are as defined above) with or without a base in an inert solvent to provide the corresponding 4-substituted amino adduct (C). The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydroxide (preferably sodium hydroxide, etc.), or a tertiary amine (preferably *N,N*-diisopropylethylamine, triethylamine, or *N*-methylemorpholine, etc.). The inert solvent includes lower alkyl alcohol solvents (preferably methanol, ethanol, 2-propanol, or butanol, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane, etc.), or amide solvents (preferably *N,N*-dimethylformamide or 1-methyl-pyrrolidin-2-one, etc.). Reaction temperature ranges from about 0°C to 200°C, preferably about 10°C to 150°C.

In turn, this is substituted by the mono-protected diamine (R₄HN-A-NR₅P, wherein R₄HN-A-NR₅P is as defined below, R₄ and R₅ are as defined above, and P is a protective group) with or without a base in an inert solvent to provide 2,4-disubstituted amino quinazoline (D). The base includes an alkali metal carbonate (preferably sodium carbonate

or potassium carbonate, etc.), an alkali metal hydroxide (preferably sodium hydroxide, etc.), or a tertiary amine (preferably *N,N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.). The inert solvent includes lower alkyl alcohol solvents (preferably methanol, ethanol, 2-propanol, or butanol, etc.) or amide solvents (preferably *N,N*-dimethylformamide or 1-methyl-pyrrolidin-2-one, etc.). Reaction temperature ranges from about 50°C to 200°C, preferably about 80°C to 150°C. Also this reaction can be carried out under microwave conditions. Representative protecting groups suitable for a wide variety of synthetic transformations are disclosed in Greene and Wuts, *Protective Groups in Organic Synthesis*, second edition, John Wiley & Sons, New York, 1991, the disclosure of which is incorporated herein by reference in its entirety. The deprotection of the protective group leads to the common intermediate (E) of the novel substituted quinazolines.

Scheme 1


$$R_4HN-A-NR_5P \text{ is ;}$$


The conversion of the common intermediate (E) to the novel substituted quinazolines (F-H) of the present invention is outlined in Scheme 2.

The amine (E) is reacted with a sulfonyl chloride (R_1SO_2Cl) and a base in an inert solvent to provide the novel sulfonamide (F) of the present invention. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydrogencarbonate (preferably sodium hydrogencarbonate or potassium hydrogencarbonate, etc.), an alkali hydroxide (preferably sodium hydroxide or potassium hydroxide, etc.), a tertiary amine (preferably *N,N*-diisopropylethylamine, triethylamine, or *N*-methymorpholine, etc.), or an aromatic amine (preferably pyridine or imidazole, etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), alcohol solvents (preferably 2-propanol, etc.), or aromatic solvents (preferably toluene or pyridine, etc.). Reaction temperature ranges from about $-20^{\circ}C$ to $50^{\circ}C$, preferably about $0^{\circ}C$ to $40^{\circ}C$.

The amine (E) is reacted with a carboxylic acid (R_1CO_2H) and a dehydrating condensing agent in an inert solvent with or without a base to provide the novel amide (G) of the present invention. The dehydrating condensing agent includes dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl), bromo-tris-pyrrolidino-phosnium hexafluorophosphate (PyBroP), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), or 1-cyclohexyl-3-methylpolystyrene-carbodiimide. The base includes a tertiary amine (preferably *N,N*-diisopropylethylamine or triethylamine, etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), nitrile solvents (preferably acetonitrile, etc.), or amide solvents (preferably *N,N*-dimethylformamide, etc.). In case of need, 1-hydroxybenzotriazole (HOBt), HOBt-6-carboxamidomethyl polystyrene, or 1-hydroxy-7-azabenzotriazole (HOAT) can be used as a reactant agent. Reaction temperature ranges from about $-20^{\circ}C$ to $50^{\circ}C$, preferably about $0^{\circ}C$ to $40^{\circ}C$.

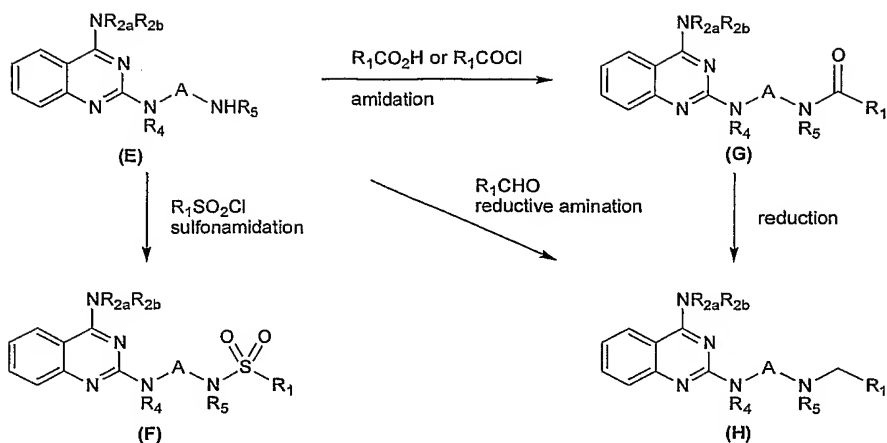
Alternatively, the novel amide (G) of the present invention can be obtained by amidation reaction using an acid chloride (R_1COCl) and a base in an inert solvent. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydrogencarbonate (preferably sodium hydrogencarbonate or

potassium hydrogencarbonate, etc.), an alkali hydroxide (preferably sodium hydroxide or potassium hydroxide, etc.), a tertiary amine (preferably *N,N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.), or an aromatic amine (preferably pyridine, imidazole, poly-(4-vinylpyridine), etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), amide solvents (preferably *N,N*-dimethylformamide, etc.), or aromatic solvents (preferably toluene or pyridine, etc.). Reaction temperature ranges from about -20°C to 50°C, preferably about 0°C to 40°C.

The novel amide (G) of the present invention is reacted with a reducing agent in an inert solvent to provide the novel amine (H) of the present invention. The reducing agent includes alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal borohydrides (preferably lithium borohydride), alkali metal trialkoxyaluminum hydrides (preferably lithium tri-*tert*-butoxyaluminum hydride), dialkylaluminum hydrides (preferably di-isobutylaluminum hydride), borane, dialkylboranes (preferably di-isoamyl borane), alkali metal trialkylboron hydrides (preferably lithium triethylboron hydride). The inert solvent includes ethereal solvents (preferably tetrahydrofuran or dioxane) or aromatic solvents (preferably toluene, etc.). Reaction temperature ranges from about -78°C to 200°C, preferably about 50°C to 120°C.

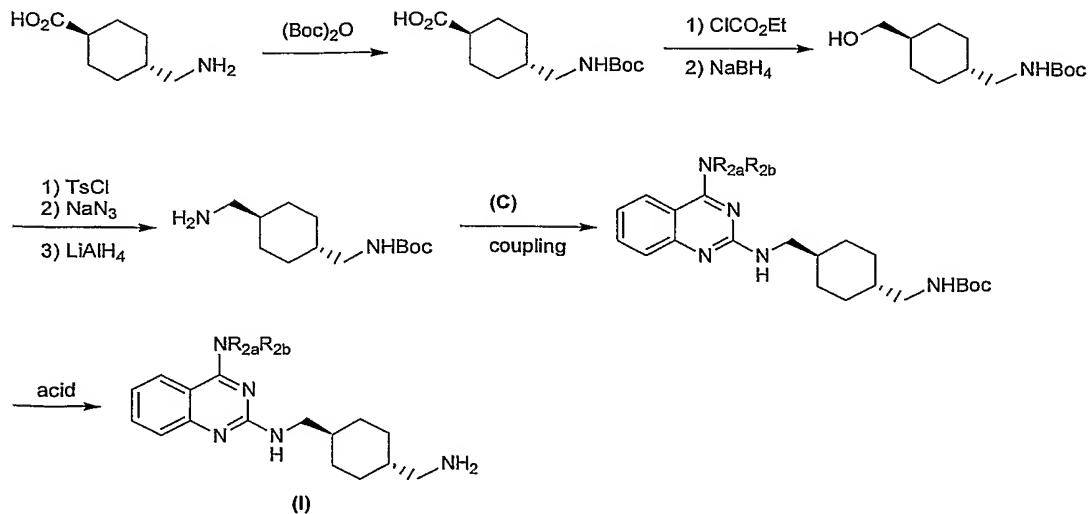
Alternatively, the novel amine (H) of the present invention can be obtained by reductive amination reaction using aldehyde (R_1CHO) and a reducing agent in an inert solvent with or without an acid. The reducing agent includes sodium triacetoxyborohydride, sodium cyanoborohydride, sodium borohydride, or boran-pyridine complex, preferably sodium triacetoxyborohydride or sodium cyanoborohydride. The inert solvent includes lower alkyl alcohol solvents (preferably methanol or ethanol, etc.), lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), or aromatic solvents (preferably toluene, etc.). The acid includes an inorganic acid (preferably hydrochloric acid or sulfuric acid) or an organic acid (preferably acetic acid). Reaction temperature ranges from about -20°C to 120°C, preferably about 0°C to 100°C. Also this reaction can be carried out under microwave conditions.

Scheme 2

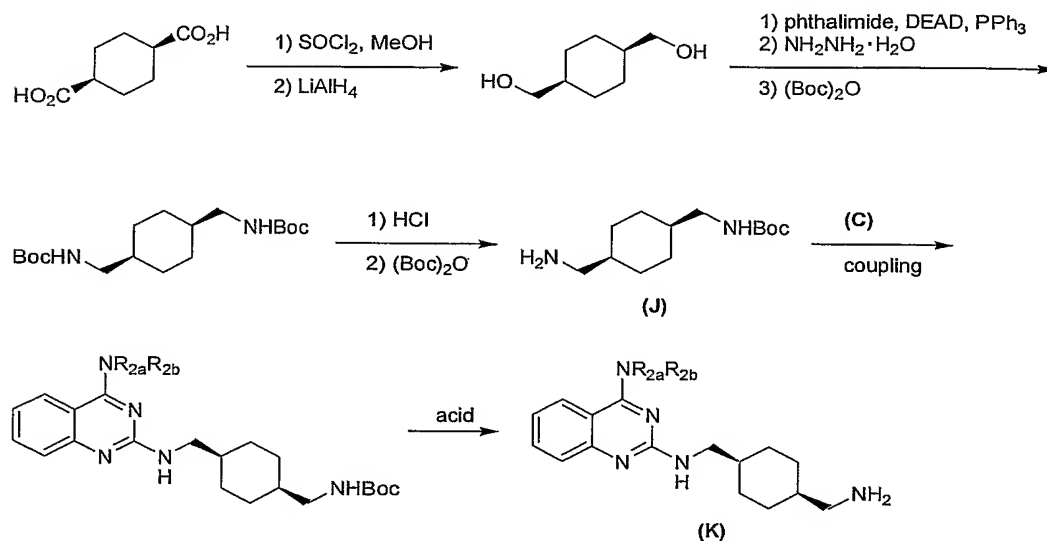


Compounds of Formula (I) can be prepared as shown in Scheme 3. The amine of commercially available *trans*-4-aminomethyl-cyclohexanecarboxylic acid is protected as *tert*-butyl carbamate. The carboxylic acid is reduced to the alcohol by sodium borohydride via the mixed acid anhydride. Tosylation of the alcohol with tosylchloride followed by azidation give the azide, which is converted to the amine by lithium aluminum hydride reduction. The coupling of the amine with the quinazoline core (C), which is synthesized in Scheme 1, gives 2,4-disubstituted amino quinazoline. The deprotection of Boc-group is achieved by an acid to give compounds of Formula (I).

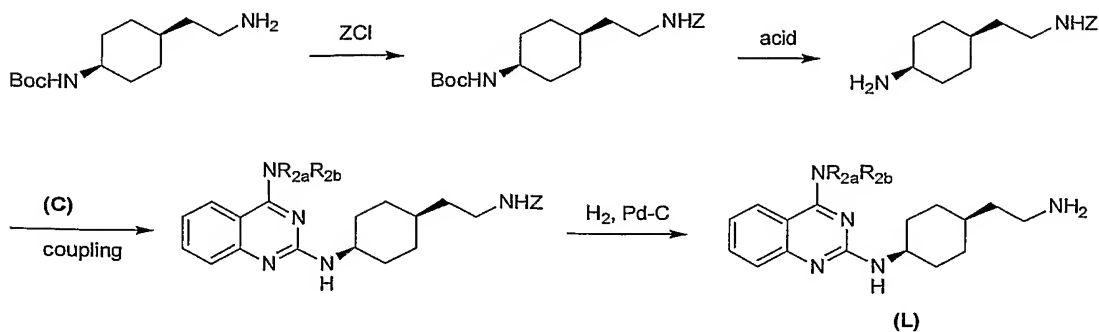
Scheme 3



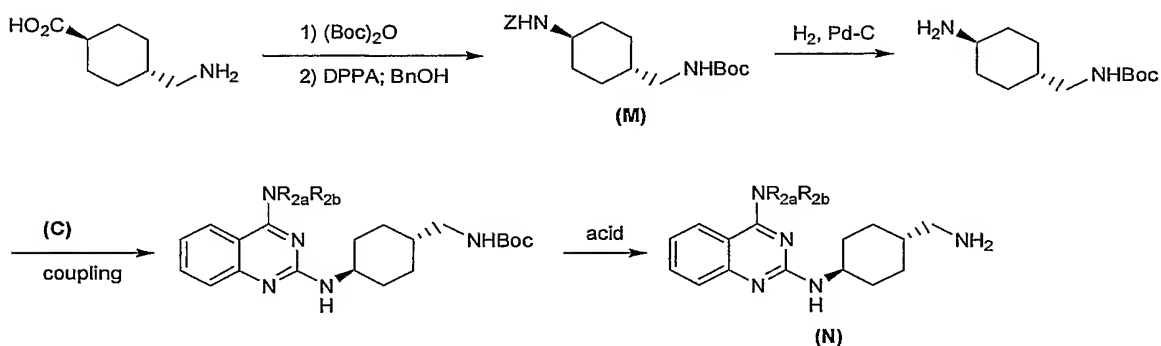
Compounds of Formula (K) can be prepared as shown in Scheme 4. Known *cis*-(4-aminomethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (J), synthesis of which is described in WO 01/72710, can be led to compounds of Formula (K) according to the method of scheme 3.

Scheme 4

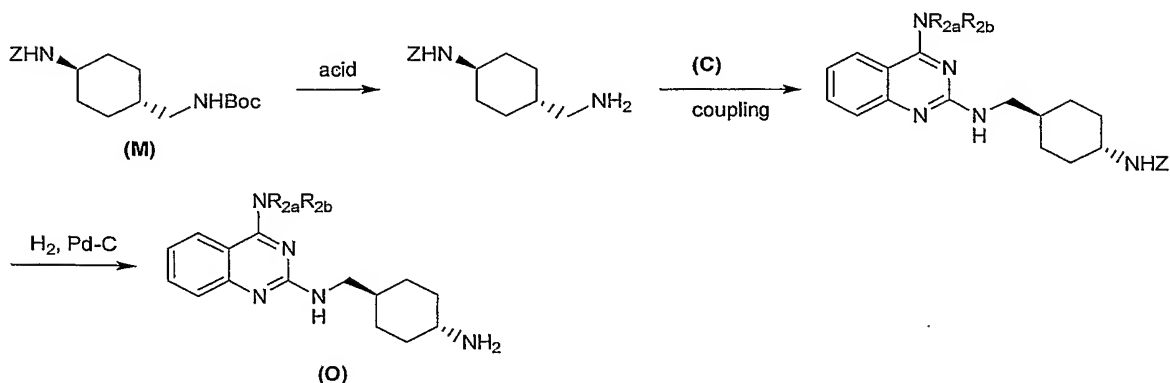
Compounds of Formula (L) can be prepared as shown in Scheme 5. The amine of *cis*-[4-(2-amino-ethyl)-cyclohexyl]-carbamic acid *tert*-butyl ester is protected as benzyl carbamate. The deprotection of Boc-group is achieved by an acid to give the amine. The coupling of the amine with quinazoline core (C), which is synthesized as scheme 1, gives 2,4-disubstituted amino quinazoline. The deprotection of Z-group is achieved by hydrogen reduction to give compounds of Formula (L).

Scheme 5

Compounds of Formula (N) can be prepared as shown in Scheme 6. The amine of commercially available *trans*-4-aminomethyl-cyclohexanecarboxylic acid is protected as *tert*-butyl carbamate. The carboxylic acid is transformed to benzyl carbamate (M) by curtius rearrangement. The deprotection of Z-group is achieved by hydrogen reduction to give the amine. The amine is converted to compounds of Formula (N) according to the method of scheme 3.

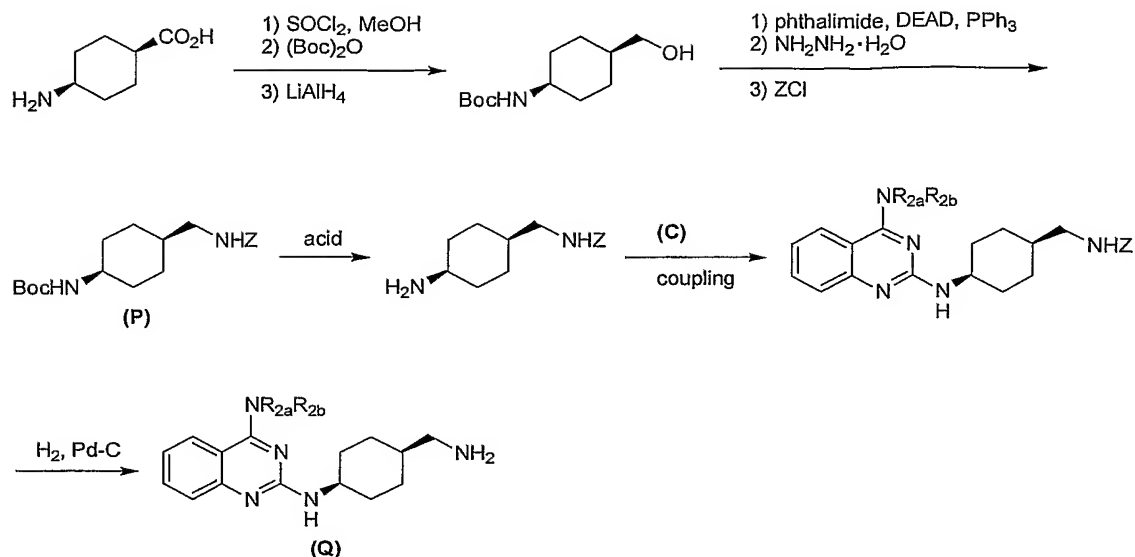
Scheme 6

Compounds of Formula (O) can be prepared from the compound of Formula (M), which is described in Scheme 6, as shown in Scheme 7. The compound of Formula (M) can be led to compounds of Formula (O) according to the method of scheme 5.

Scheme 7

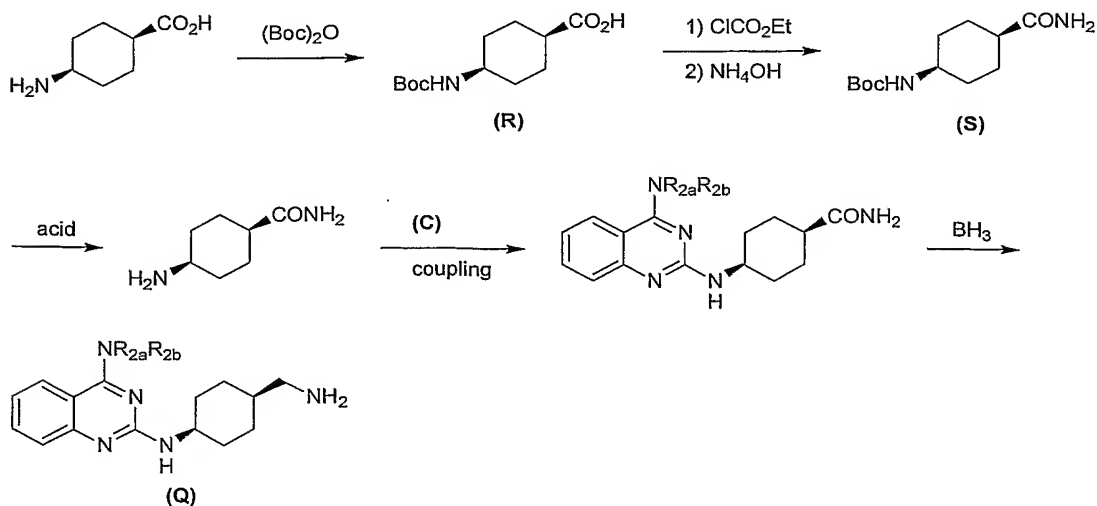
Compounds of Formula (Q) can be prepared as shown in Scheme 8. [4-(Benzyloxycarbonylamino-methyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (P), synthesis of which is described in WO 01/72710, can be led to compounds of Formula (Q) according to the method of scheme 5.

Scheme 8

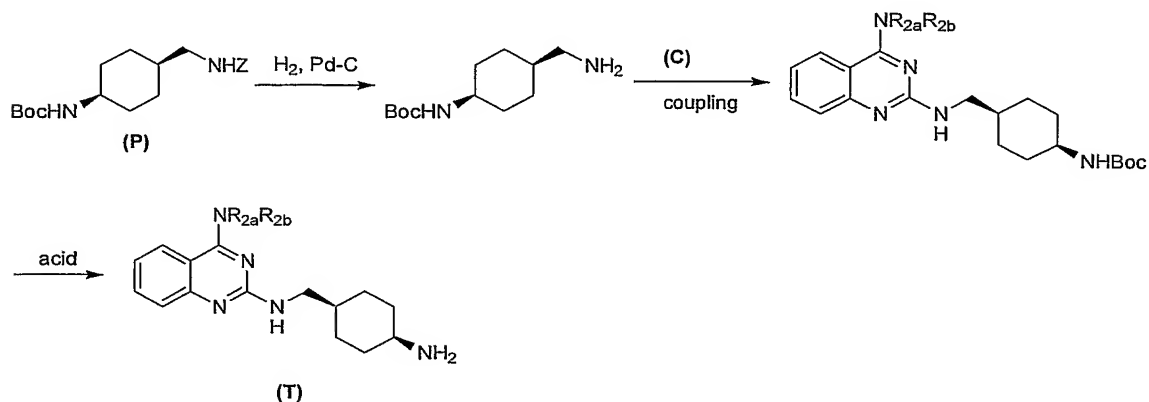


Alternatively compounds of Formula (Q) can be prepared as shown in Scheme 9. The amine of commercially available *cis*-4-amino-cyclohexanecarboxylic acid is protected as *tert*-butyl carbamate. The carboxylic acid (R) is converted to the amide (S) by aqueous ammonia via the mixed acid anhydride. The deprotection of Boc-group is achieved by an acid to give the amine. The coupling of the amine with quinazoline core (C), which is synthesized as scheme 1, gives 2,4-disubstituted amino quinazoline. The amide is reduced to compounds of Formula (Q).

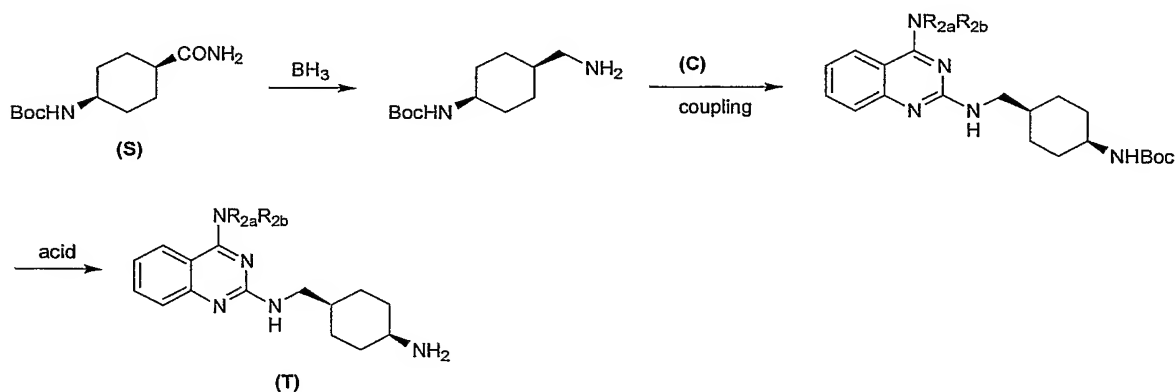
Scheme 9



Compounds of Formula (T) can be prepared from the compound of Formula (P), which is described in Scheme 8, as shown in Scheme 10. The compound of Formula (P) can be led to compounds of Formula (T) according to the method of scheme 6.

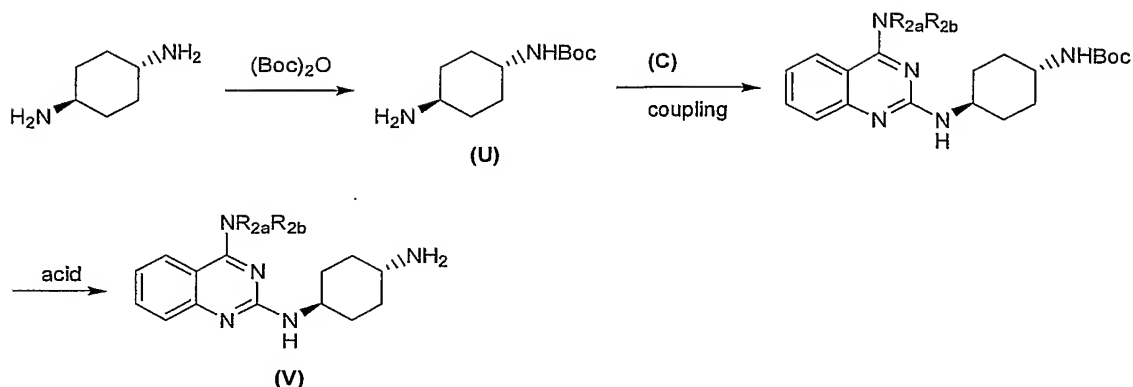
Scheme 10

Alternatively compounds of Formula (T) can be prepared as shown in Scheme 11. The amide (S), which is described in Scheme 9, is reduced to the amine. The amine can be led to compounds of Formula (T) according to the method of scheme 3.

Scheme 11

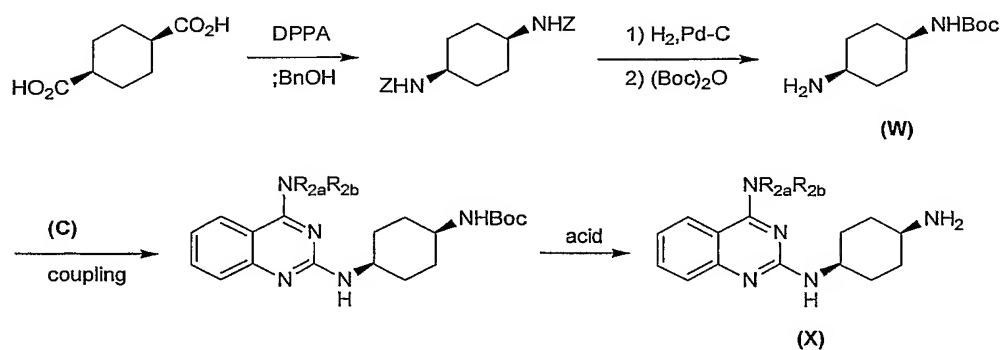
Compounds of Formula (V) can be prepared as shown in Scheme 12. The mono-protection of commercially available *trans*-cyclohexane-1,4-diamine can be achieved by the method described in *Synthetic communications*, **20**, 2559-2564 (1990). The conversion to compounds of Formula (V) can be accomplished according to the method of scheme 3.

Scheme 12



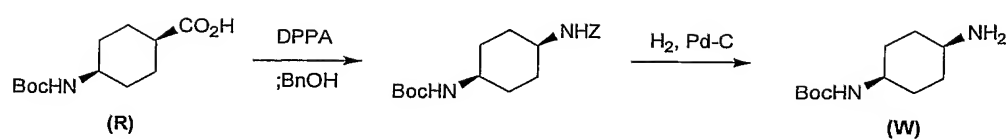
Compounds of Formula (X) can be prepared as shown in Scheme 13. The dicarboxylic acid of commercially available *cis*-cyclohexane-1,4-dicarboxylic acid is transformed to dibenzyl carbamate by curtius rearrangement. The deprotection of Z-group is achieved by hydrogen reduction to give the diamine. The mono-protection of the diamine can be achieved according to the method of scheme 12 to give the compound (W). The conversion to compounds of Formula (X) can be accomplished according to the method of scheme 3.

Scheme 13



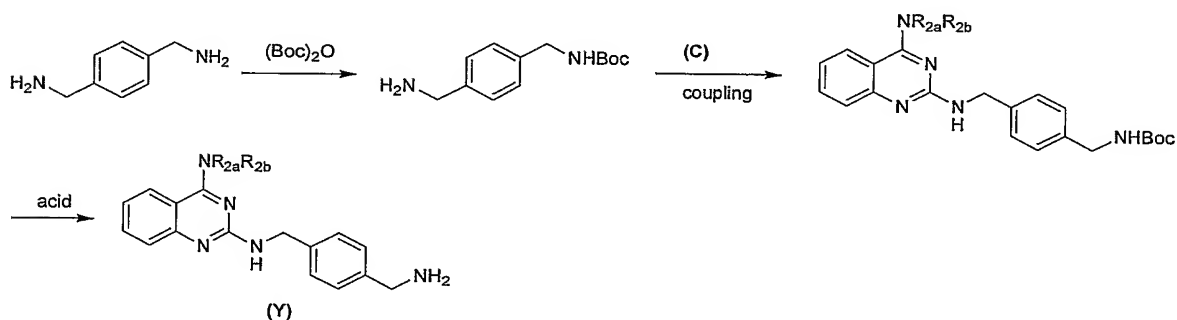
Alternatively the compound of Formula (W) can be prepared as shown in Scheme 14. The carboxylic acid (R), which is described in Scheme 9, is transformed to benzyl carbamate by curtius rearrangement. The deprotection of Z-group is achieved by hydrogen reduction to give the compound of Formula (W).

Scheme 14



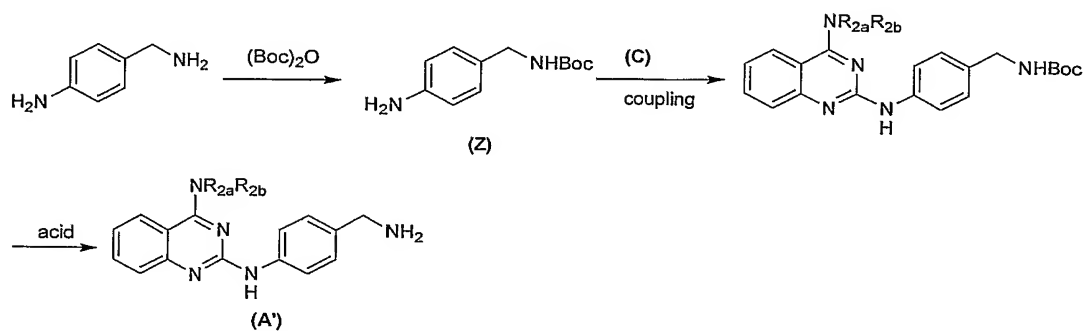
Compounds of Formula (Y) can be prepared according to the method described in Scheme 12 by using commercially available 4-aminomethyl-benzylamine as a starting material (Scheme 15).

Scheme 15



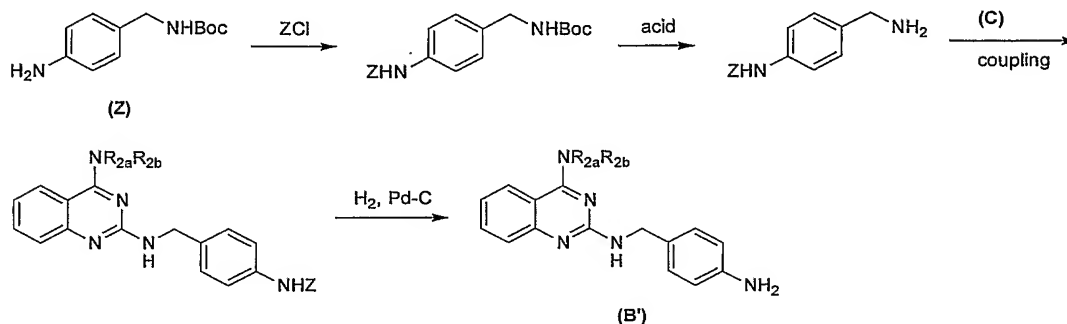
Compounds of Formula (A') can be prepared as shown in Scheme 16. The mono-protection of commercially available 4-aminomethyl-phenylamine can be achieved by using an equimolecular amount of (Boc)₂O to give mono-*tert*-butyl carbamate (Z). The amine can be led to compounds of Formula (A') according to the method of scheme 3.

Scheme 16



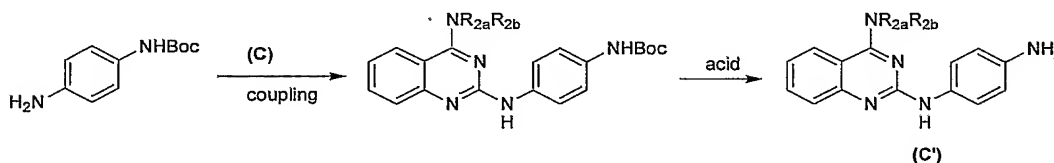
Compounds of Formula (B') can be prepared from the compound of Formula (Z), which is described in Scheme 16, as shown in Scheme 17. The compound of Formula (Z) can be led to compounds of Formula (B') according to the method of scheme 5.

Scheme 17



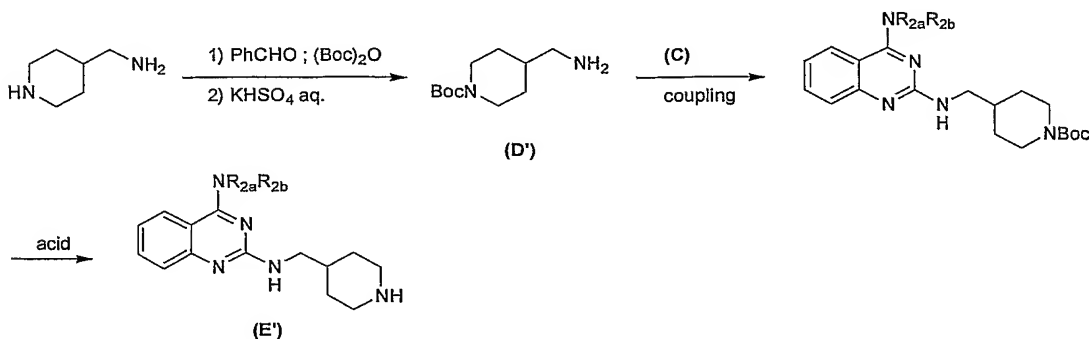
Compounds of Formula (C') can be prepared according to the method described in Scheme 3 by using commercially available (4-amino-phenyl)-carbamic acid *tert*-butyl ester as a starting material (Scheme 18).

Scheme 18



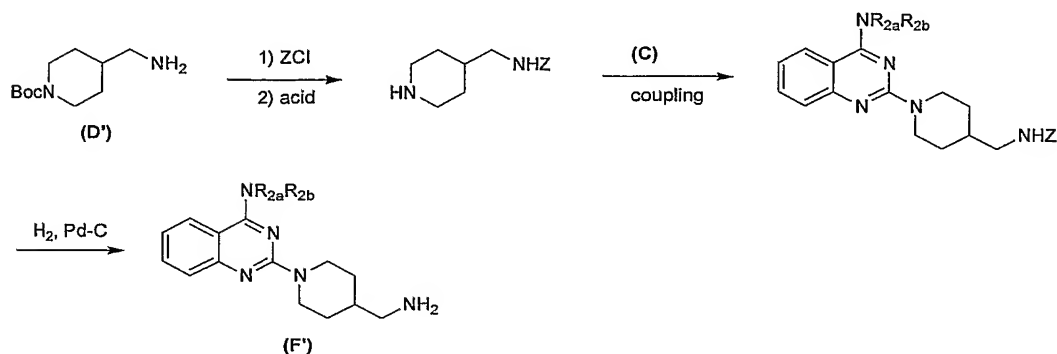
Compounds of Formula (E') can be prepared as shown in Scheme 19. The selective protection of the secondary amine in the presence of the primary amine of commercially available 4-(aminomethyl)piperidin is achieved by the method described in *Synthetic communications*, **22**, 2357-2360 (1992) to give the amine (D'). The amine is converted to compounds of Formula (E') according to the method of scheme 3.

Scheme 19



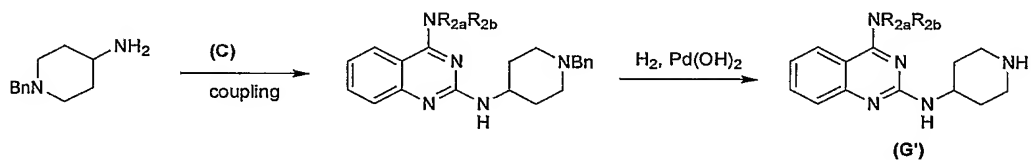
Compounds of Formula (F') can be prepared from the compound of Formula (D'), which is described in Scheme 19, as shown in Scheme 20. The compound of Formula (D') can be led to compounds of Formula (F') according to the method of Scheme 5.

Scheme 20



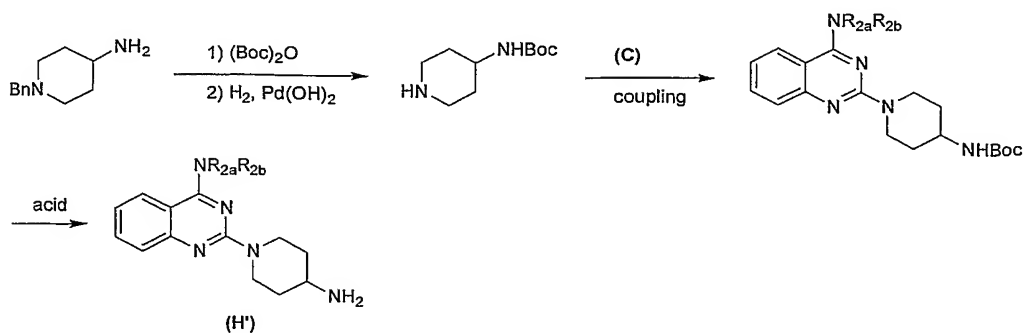
Compounds of Formula (G') can be prepared according to the method described in Scheme 5 by using commercially available 1-benzyl-piperidin-4-ylamine as a starting material (Scheme 21).

Scheme 21



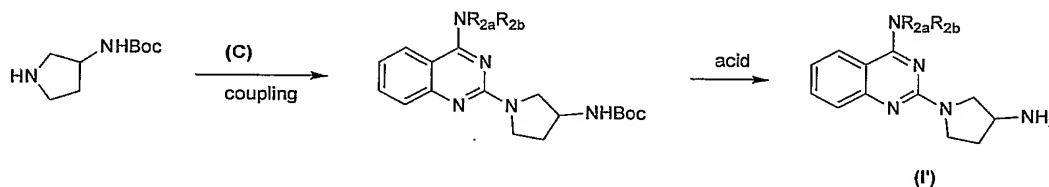
Compounds of Formula (H') can be prepared as shown in Scheme 22. The amine of commercially available 1-benzyl-piperidin-4-ylamine is protected as *tert*-butyl carbamate. The deprotection of benzyl group is achieved by hydrogen reduction to give the amine. The amine can be led to compounds of Formula (H') according to the method of scheme 3.

Scheme 22



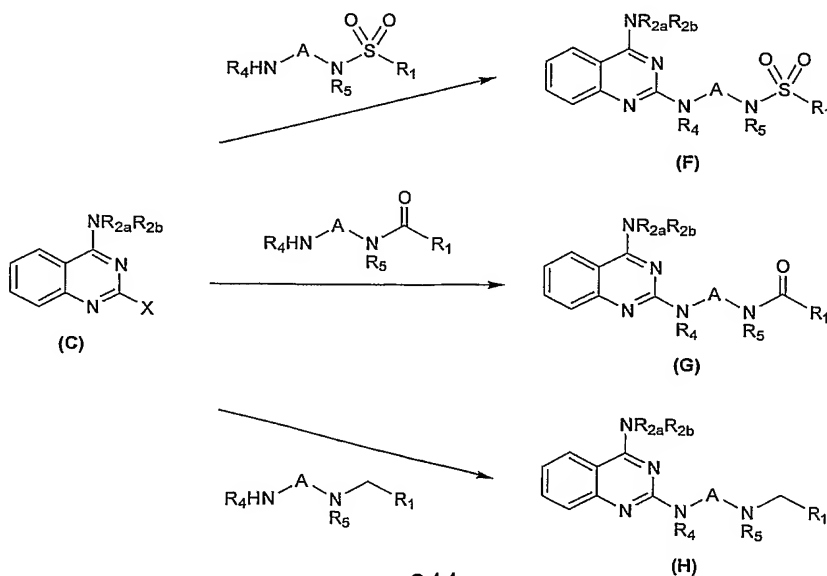
Compounds of Formula (I') can be prepared according to the method described in Scheme 3 by using commercially available pyrrolidin-3-yl-carbamic acid *tert*-butyl ester as a starting material (Scheme 23).

Scheme 23



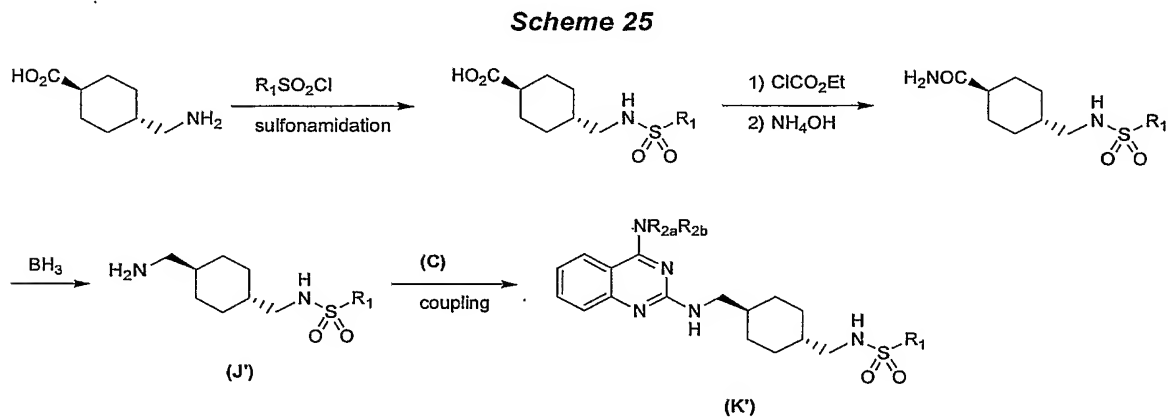
Alternatively, the novel sulfonamide (F), the novel amide (G), and the novel amine (H) of the present invention are directly synthesized from the quinazoline core (C), which is synthesized in Scheme 1, as shown in Scheme 24. This coupling is performed with or without a base in an inert solvent. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydroxide (preferably sodium hydroxide, etc.), or a tertiary amine (preferably *N,N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.). The inert solvent includes lower alkyl alcohol solvents (preferably methanol, ethanol, 2-propanol, or butanol, etc.) or amide solvents (preferably *N,N*-dimethylformamide or 1-methyl-pyrrolidin-2-one, etc.). Reaction temperature ranges from about 50°C to 200°C, preferably about 80°C to 180°C. Also this reaction can be carried out under microwave conditions.

Scheme 24

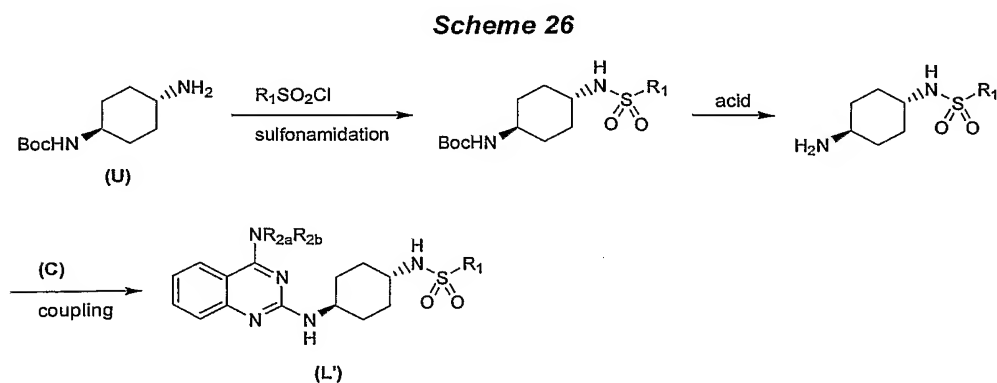


Compounds of Formula (K') can be prepared as shown in Scheme 25.

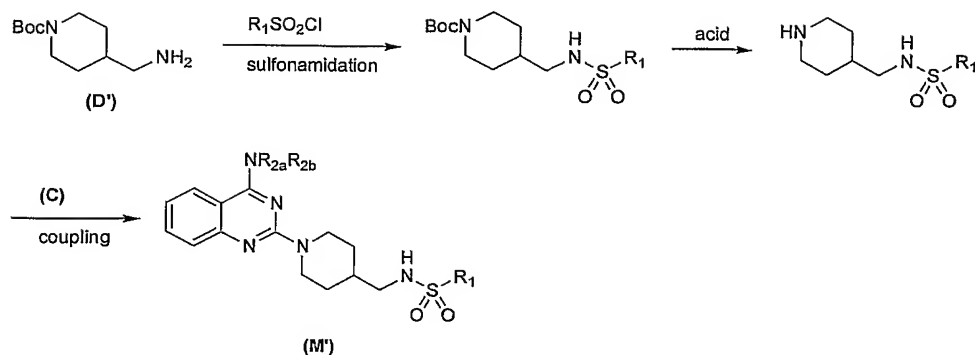
Commercially available *trans*-4-aminomethyl-cyclohexanecarboxylic acid is reacted with sulfonyl chloride (R_1SO_2Cl) to give the sulfonamide. The carboxylic acid is converted to the amide via the mixed acid anhydride. The amide is reduced to the amine (J') by borane reduction. The coupling of the amine with the quinazoline core (C), which is synthesized in Scheme 1, gives the novel sulfonamide (K') of the present invention.



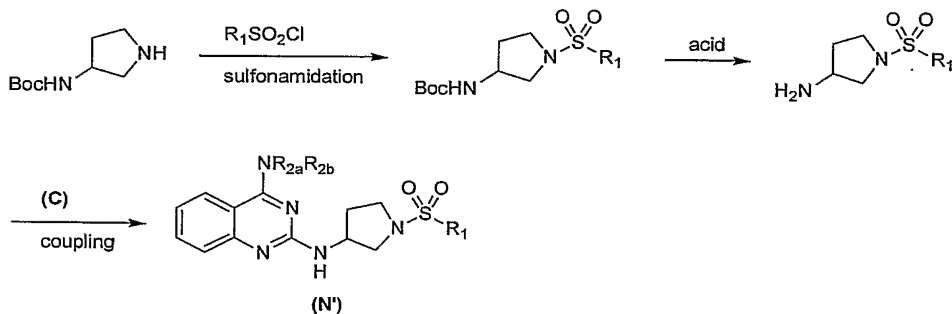
Compounds of Formula (L') can be prepared from the compound of Formula (U), which is described in Scheme 12, as shown in Scheme 26. The amine (U) is reacted with sulfonyl chloride (R_1SO_2Cl) to give the sulfonamide. The deprotection of Boc-group is achieved by an acid to give the amine. The coupling of the amine with quinazoline core (C), which is synthesized as scheme 1, gives the novel sulfonamide (L') of the present invention.



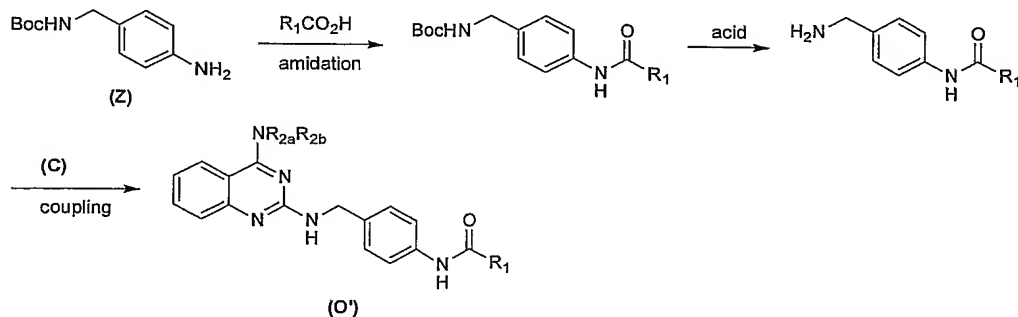
Compounds of Formula (M') can be prepared according to the method described in Scheme 26 by using the compound of Formula (D'), which is described in Scheme 19, as a starting material (Scheme 27).

Scheme 27

Compounds of Formula (N') can be prepared according to the method described in Scheme 26 by using commercially available pyrrolidin-3-yl-carbamic acid *tert*-butyl ester as a starting material (Scheme 28).

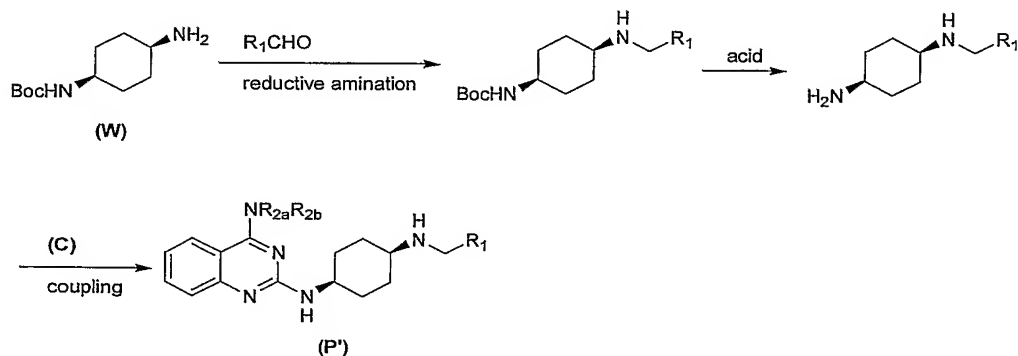
Scheme 28

Compounds of Formula (O) can be prepared from the compound of Formula (Z), which is described in Scheme 16, as shown in Scheme 29. The aniline (Z) is reacted with carboxylic acid (R_1CO_2H) to give the amide. The deprotection of Boc-group is achieved by an acid to give the amine. The coupling of the amine with quinazoline core (C), which is synthesized as scheme 1, gives the novel sulfonamide (O') of the present invention.

Scheme 29

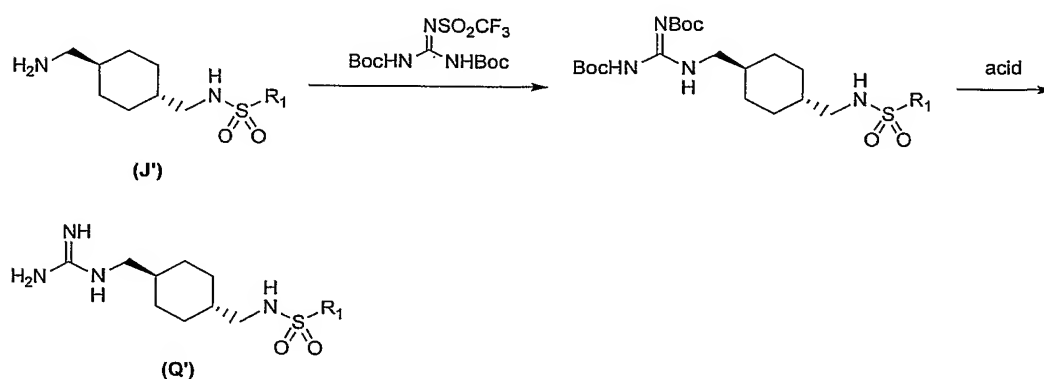
Compounds of Formula (P') can be prepared as shown in Scheme 30. The amine (W), which is synthesized in Scheme 13, is subjected to reductive amination by aldehyde ($R_1\text{CHO}$). The deprotection of Boc-group is achieved by an acid to give the amine. The coupling of the amine with quinazoline core (C), which is synthesized as scheme 1, gives the novel amine (P') of the present invention.

Scheme 30



Scheme 31 shows the preparation of compounds (Q') of the invention where Q of Formula I has Formula III. The compound (J'), which is synthesized in Scheme 25, is reacted with (1-*tert*-butoxycarbonylimino-1-trifluoromethanesulfonylimino-methyl)-carbamic acid *tert*-butyl ester. The deprotection of Boc-group is achieved by an acid to give the novel guanidine (Q') of the present invention.

Scheme 31



Examples

The compounds of the invention and their synthesis are further illustrated by the following examples. The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples. "Ambient temperature" as referred to in the following example is meant to indicate a temperature falling between 0 °C and 40 °C.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows :

¹H NMR : proton nuclear magnetic resonance spectrum

AcOH : acetic acid

APCI : atmospheric pressure chemical ionization

(Boc)₂O : di-tertiary-butyl dicarbonate

BuLi : butyl lithium

BuOH : butanol

CaCl₂ : calcium chloride

CDCl₃ : deuterated chloroform

CF₃CO₂H : trifluoroacetic acid

CH₂Cl₂ : dichloromethane

CHCl₃ : chloroform

CI : chemical ionization

CuCl : copper (I) chloride

D₂O : deuterium oxide

DMAP : 4-dimethylaminopyridine

DMF : *N,N*-dimethylformamide

DMSO : dimethyl sulfoxide

EDC : 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

ESI : electrospray ionization

Et₂O : diethyl ether

EtOAc : acetic acid ethyl ester

EtOH : ethanol

FAB : fast atom bombardment

H₂SO₄ : sulfuric acid

HATU : *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-

hexafluorophosphate
HCHO : formaldehyde
HCl : hydrogen chloride
HOAt : 1-hydroxy-7-azabenzotriazole
HOBt : 1-hydroxybenzotriazole
HPLC : high performance liquid chromatography
 K_2CO_3 : potassium carbonate
 $KHSO_4$: potassium bisulfate
 Me_2NH : dimethylamine
 $MeNH_2$: methylamine
MeOH : methanol
 $MgSO_4$: magnesium sulfate
 Na_2CO_3 : sodium carbonate
 $Na_2SO_4 \cdot 10H_2O$: sodium sulfate decahydrate
 $NaBH(OAc)_3$: sodium triacetoxyborohydride
 $NaBH_3CN$: sodium cyanoborohydride
 $NaBH_4$: sodium borohydride
 $NaHCO_3$: sodium hydrogencarbonate
 NaN_3 : sodium azide
 $NaNO_2$: sodium nitrate
 $Pd(OH)_2$: palladium hydroxide
Pd/C : palladium carbon
 $POCl_3$: phosphoryl chloride
PVP : poly(4-vinylpyridine)
PyBroP : bromo-tris-pyrrolidino phosphonium hexafluoro phosphate
 $SOCl_2$: thionyl chloride
t-BuOH : tertiary butanol
TFA : trifluoroacetic acid
THF : tetrahydrofuran
WSC : water solubule carbodiimide
ZCl : benzyloxycarbonyl chloride
s : singlet

d : doublet

t : triplet

q : quartet

dd : doublet doublet

dt : doublet triplet

ddd : doublet doublet doublet

brs : broad singlet

m : multiplet

J : coupling constant

Hz : Hertz

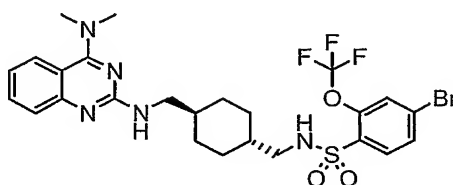
The analytical condition of high performance liquid chromatography is as follows:

Solvent A: 0.050% TFA in water

Solvent B: 0.035% TFA in acetonitrile

5 - 100% B over 5 min, flow rate 3.5 ml/min

Example 1



***trans*-4-Bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide**

Step A: Synthesis of 2,4-dichloro-quinazoline.

To a suspension of 1*H*-quinazoline-2,4-dione (150 g, 925 mmol) in POCl₃ (549 mL, 5.89 mol) was added dimethyl-phenyl-amine (123 mL, 962 mmol). The mixture was stirred at reflux for 7 hr and concentrated. The solution was poured into ice water, and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (silica gel,

50% CHCl₃ in hexane to 10% EtOAc in CHCl₃) to give 2,4-dichloro-quinazoline (159g, 86%) as a pale yellow solid.

CI MS m/e 199, M⁺; ¹H NMR (300 MHz, CDCl₃) δ 8.27 (dt, *J* = 8.3, 1.1 Hz, 1 H), 7.95-8.04 (m, 2 H), 7.71-7.81 (m, 1 H).

Step B: Synthesis of (2-chloro-quinazolin-4-yl)-dimethyl-amine.

A solution of 2,4-dichloro-quinazoline (102 g, 530 mmol) in THF (1.2 L) was cooled to 4 °C and 50% aqueous Me₂NH (139 mL, 1.33 mol) was added. The mixture was stirred at ambient temperature for 80 min. The solution was alkalized with saturated aqueous NaHCO₃ (pH = 9), and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, and concentrated. The residue was suspended in 50% Et₂O in hexane (250 mL) and stirred at ambient temperature for 30 min. The solid was collected by filtration, washed with 50% Et₂O in hexane, and dried at 80 °C to give (2-chloro-quinazolin-4-yl)-dimethyl-amine (104 g, 94%) as a pale yellow solid.

ESI MS m/e 207, M⁺; ¹H NMR (300 MHz, CDCl₃) δ 8.00 (d, *J* = 8.4 Hz, 1 H), 7.73-7.78 (m, 2 H), 7.68 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1 H), 3.41 (s, 6 H).

Step C: Synthesis of *trans*-4-(*tert*-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid.

To a solution of *trans*-4-aminomethyl-cyclohexanecarboxylic acid (150 g, 954 mmol) in 1.32 M aqueous sodium hydroxide (750 mL) were added *t*-BuOH (1680 mL) and (Boc)₂O (215 g, 985 mmol). The reaction mixture was stirred at ambient temperature for 18 hr. To the reaction mixture was added H₂O (2.8 L), and cooled at 5 °C. The aqueous layer was acidified with saturated aqueous KHSO₄ (pH = 3), extracted with EtOAc (three times). The combined organic layer was washed with saturated aqueous NaHCO₃ and brine, dried over MgSO₄, filtered, concentrated and dried under reduced pressure to give *trans*-4-(*tert*-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (165 g, 67%) as a white solid.

ESI MS m/e 280, M + Na⁺; ¹H NMR (300 MHz, CDCl₃) δ 4.60 (brs, 1 H), 2.98 (t, *J* = 6.3 Hz, 2 H), 2.19-2.33 (m, 1 H), 1.99-2.11 (m, 2 H), 1.77-1.90 (m, 2 H), 1.44 (s, 9 H), 1.34-1.52 (m, 3 H), 0.86-1.05 (m, 2 H).

Step D: Synthesis of *trans*-(4-hydroxymethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester.

A suspension of *trans*-4-(*tert*-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (155 g, 603 mmol) in CH₂Cl₂ (1.35 L) was cooled at -65 °C and triethylamine (126 mL, 904 mmol) and a solution of ethyl chloroformate (58 mL, 751 mmol) in CH₂Cl₂ (200 mL) were added below -60 °C. The reaction mixture was stirred at 0 °C for 50 min. The mixture was acidified with saturated aqueous KHSO₄ (pH = 3), and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was washed with saturated aqueous Na₂CO₃ and brine, dried over MgSO₄, filtered, and concentrated to give a colorless oil. A solution of the above oil in THF (1.5 L) was cooled at -65 °C and NaBH₄ (26.6 g, 703 mmol) and MeOH (45 mL) were added. The mixture was stirred at -40 °C for 25 min, and stirred at 4 °C for 3 hr. The mixture was acidified with saturated aqueous KHSO₄ (pH = 3), and the aqueous layer was extracted with EtOAc (three times). The combined organic layer was washed with saturated aqueous Na₂CO₃ and brine, dried over MgSO₄, filtered, and concentrated, and purified by flash chromatography (silica gel, 17% MeOH in CHCl₃) to give *trans*-(4-hydroxymethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (123 g, 84%) as a white solid.

ESI MS *m/e* 266, M + Na⁺; ¹H NMR (300 MHz, CDCl₃) δ 4.59 (brs, 1 H), 3.46 (d, *J* = 6.4 Hz, 2 H), 2.98 (t, *J* = 6.3 Hz, 2 H), 1.75-1.94 (m, 4 H), 1.45 (s, 9 H), 1.24-1.70 (m, 3 H), 0.81-1.12 (m, 4 H).

Step E: Synthesis of *trans*-(4-azidomethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester.

A solution of *trans*-(4-hydroxymethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (123 g, 505 mmol) in pyridine (1 L) was cooled at 4 °C and a solution of *p*-toluenesulfonyl chloride (125 g, 657 mmol) in pyridine (200 ml) was added below 10 °C. The mixture was stirred at ambient temperature for 15 hr and concentrated. After dissolution with EtOAc and H₂O, the organic layer was separated. The aqueous layer was extracted with EtOAc (three times), the combined organic layer was washed with H₂O, dried over MgSO₄, filtered, and concentrated to give a pale yellow oil. To a solution of the above oil in DMF (1.6 L) was added NaN₃ (98.8 g, 1.52 mol). The reaction mixture was stirred at ambient temperature for 14 hr and concentrated. After dissolution with CHCl₃ and saturated aqueous NaHCO₃, the organic layer was separated. The aqueous layer was

extracted with CHCl_3 (three times), the combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by flash chromatography (silica gel, 17% EtOAc in hexane) to give *trans*-(4-azidomethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (124 g, 91%) as a colorless oil.

ESI MS m/e 291, $M + \text{Na}^+$; ^1H NMR (300 MHz, CDCl_3) δ 4.59 (brs, 1 H), 3.13 (d, $J = 6.5$ Hz, 2 H), 2.98 (t, $J = 6.4$ Hz, 2 H), 1.70-1.90 (m, 4 H), 1.44 (s, 9 H), 1.25-1.65 (m, 2 H), 0.87-1.07 (m, 4 H).

Step F: Synthesis of *trans*-(4-aminomethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester.

A suspension of lithium aluminum hydride (2.76 g, 72.6 mmol) in THF (225 mL) was cooled at 0 °C and a solution of *trans*-(4-azidomethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (15.0 g, 55.9 mmol) in THF (75 mL) was added over 1 hr. The reaction mixture was stirred at ambient temperature for 6 hr. The reaction was quenched with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$, filtered through a pad of celite, and concentrated. The residue was purified by flash chromatography (silica gel, 50% MeOH in CHCl_3) to give *trans*-(4-aminomethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (12.3 g, 91%) as a pale yellow oil.

ESI MS m/e 243, $M + \text{H}^+$; ^1H NMR (300 MHz, CDCl_3) δ 4.60 (brs, 1 H), 2.97 (t, $J = 6.3$ Hz, 2 H), 2.53 (d, $J = 6.4$ Hz, 2 H), 1.70-1.92 (m, 4 H), 1.44 (s, 9 H), 1.08-1.54 (m, 4 H), 0.81-1.02 (m, 4 H).

Step G: Synthesis of *trans*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester.

A mixture of (2-chloro-quinazolin-4-yl)-dimethyl-amine (15.2 g, 73.3 mmol) and *trans*-(4-aminomethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (14.8 g, 61.0 mmol) in 2-propanol (80 mL) was stirred at reflux for 4 days, poured into saturated aqueous NaHCO_3 , and the aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by flash chromatography (NH-silica gel, 33% EtOAc in hexane) to give *trans*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester (20.4 g, 81%) as a pale yellow solid.

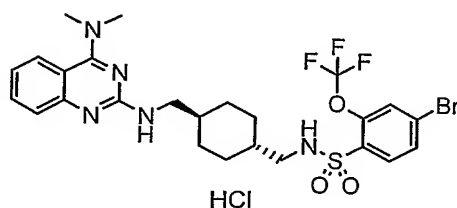
ESI MS m/e 414, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, $J = 8.2$ Hz, 1 H), 7.40-7.52 (m, 2 H), 6.98-7.06 (m, 1 H), 4.93 (brs, 1 H), 4.59 (brs, 1 H), 3.35 (t, $J = 6.2$ Hz, 2 H), 3.26 (s, 6 H), 2.97 (t, $J = 6.2$ Hz, 2H), 1.72-1.95 (m, 4H), 1.44 (s, 9H), 1.30-1.62 (m, 2H), 0.84-1.12 (m, 4H).

Step H: Synthesis of *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide hydrochloride.

To a suspension of *trans*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]cyclohexylmethyl}-carbamic acid *tert*-butyl ester (3.84 g, 9.28 mmol) in EtOAc (50 mL) was added 4 M hydrogen chloride in EtOAc (38 mL). The mixture was stirred at ambient temperature for 40 min and concentrated to give a white solid. To a suspension of the solid in CH_2Cl_2 (50 mL) was added diisopropylethylamine (6.46 mL, 37.1 mmol). The mixture was cooled at 4 °C and a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (3.31 g, 9.75 mmol) in CH_2Cl_2 (10 mL) was added below 5 °C. The reaction mixture was stirred at 4 °C for 1.5 hr. The reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 20% EtOAc in hexane) to give *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide (3.45 g, 60%) as a pale yellow solid.

ESI MS m/e 616, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, $J = 8.9$ Hz, 1 H), 7.81 (d, $J = 7.6$ Hz, 1 H), 7.35-7.61 (m, 4 H), 7.02 (t, $J = 6.8$ Hz, 1 H), 4.96 (brs, 1 H), 3.35 (t, $J = 6.1$ Hz, 2 H), 3.26 (s, 6 H), 2.79 (d, $J = 6.7$ Hz, 2 H), 1.32-1.98 (m, 6 H), 0.72-1.12 (m, 4 H).

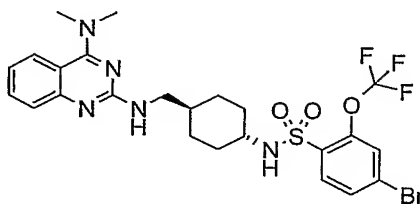
Example 2



***trans*-4-Bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-**

cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide hydrochloride**Step A: Synthesis of *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide hydrochloride.**

A solution of *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide obtained step H of example 1 (3.45 g, 5.61 mmol) in EtOAc (100 mL) was cooled on an ice-bath and 4 M hydrogen chloride in EtOAc (1.66 mL) was added. The mixture was stirred at ambient temperature for 1 hr and concentrated to give a white solid. The solid was recrystallized from 16% EtOH in Et₂O, and dried under reduced pressure to give *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide hydrochloride (2.76g, 75%) as a white solid. ESI MS *m/e* 616, *M* + *H*⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.50 (brs, 1H), 8.42 (t, *J* = 6.0 Hz, 1 H), 7.86-7.94 (m, 2 H), 7.51-7.68 (m, 4H), 7.21-7.28 (m, 1 H), 4.83 (d, *J* = 6.4 Hz, 1 H), 3.51 (s, 6 H), 3.35 (t, *J* = 6.0 Hz, 2H), 2.78 (t, *J* = 6.4 Hz, 2H), 1.73-1.95 (m, 4H), 1.35-1.65 (m, 2H), 0.81-1.12 (m, 4H).

Example 3***trans*-4-Bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexyl}-2-trifluoromethoxy-benzenesulfonamide****Step A: Synthesis of *trans*-[4-(*tert*-butoxycarbonylamino-methyl)-cyclohexyl]-carbamic acid benzyl ester.**

To a suspension of *trans*-4-aminomethyl-cyclohexanecarboxylic acid (15.0 g, 95.4 mmol) in CHCl₃ (150 mL) were added 1 M aqueous sodium hydroxide (150 mL) and (Boc)₂O (21.9 g, 100 mmol) successively. The reaction mixture was stirred at ambient

temperature for 15 hr, and partitioned between CHCl_3 and water. The aqueous layer was acidified with saturated aqueous KHSO_4 ($\text{pH} = 3$), extracted with CHCl_3 (three times). The combined organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated to give a white solid. To a suspension of the above solid in benzene (75 mL) were added phosphorazidic acid diphenyl ester (16.2 g, 58.9 mmol) and triethylamine (5.94 g, 58.7 mmol). The reaction mixture was stirred at reflux for 3 hr (**Caution! Vigorous exothermic reaction**). Benzyl alcohol (6.65 g, 61.5 mmol) was added, the reaction mixture was stirred at reflux for 24 hr, concentrated. After dissolution with EtOAc and H_2O , the organic layer was separated. The aqueous layer was extracted with EtOAc (twice), the combined organic layer was washed with 1 M aqueous KHSO_4 , saturated aqueous NaHCO_3 and brine, dried over MgSO_4 , filtered, concentrated, and purified by flash chromatography (silica gel, 33% EtOAc in hexane) to give a white solid. A suspension of the above solid in Et_2O was stirred at ambient temperature for 30 min and filtered. The filtrate was washed with Et_2O and dried under reduced pressure to give *trans*-[4-(*tert*-butoxycarbonylamino-methyl)-cyclohexyl]-carbamic acid benzyl ester (17.4 g, 50%) as a white solid.

ESI MS m/e 385, $\text{M} + \text{Na}^+$; ^1H NMR (300 MHz, CDCl_3) δ 7.22-7.41 (m, 5 H), 5.09 (s, 2 H), 4.20-4.68 (m, 2 H), 3.23-3.60 (m, 1 H), 2.96 (t, 2 H, $J = 6.4$ Hz), 1.62-2.18 (m, 4 H), 1.44 (s, 9 H), 1.30-1.60 (m, 1 H), 0.90-1.23 (m, 4 H).

Step B: Synthesis of *trans*-(4-aminomethyl-cyclohexyl)-carbamic acid benzyl ester hydrochloride.

To a suspension of *trans*-[4-(*tert*-butoxycarbonylamino-methyl)-cyclohexyl]-carbamic acid benzyl ester (4.00 g, 11.0 mmol) in EtOAc (40 mL) was added 4 M hydrogen chloride in EtOAc (10 mL). To the reaction mixture was added CHCl_3 (10 mL) and the mixture was stirred at ambient temperature for 3 hr. To the reaction mixture was 4 M hydrogen chloride in EtOAc (20 mL) and the mixture was stirred at ambient temperature for 1.5 hr, filtered, washed with EtOAc, and dried under reduced pressure to give *trans*-(4-aminomethyl-cyclohexyl)-carbamic acid benzyl ester hydrochloride (2.96 g, 90%) as a white solid.

ESI MS m/e 263, $\text{M} (\text{free}) + \text{H}^+$; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.12 (brs, 3 H), 7.25-7.40 (m, 5 H), 7.21 (d, 1 H, $J = 7.8$ Hz), 5.00 (s, 2 H), 3.17-3.30 (m, 1 H), 2.62 (d, 2 H, $J = 7.0$ Hz), 1.64-1.88 (m, 4 H), 1.42-1.60 (m, 1 H), 0.90-1.21 (m, 4 H).

Step C: Synthesis of *trans*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexyl}-carbamic acid benzyl ester .

A mixture of (2-chloro-quinazolin-4-yl)-dimethyl-amine (1.50 g, 7.22 mmol) and *trans*-(4-aminomethyl-cyclohexyl)-carbamic acid benzyl ester hydrochloride (2.59 g, 8.67 mmol) in 2-propanol (15 mL) was stirred at reflux for 8 days and dissolved in CHCl_3 and MeOH. The mixture was poured into saturated aqueous NaHCO_3 , and the aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by flash chromatography (NH-silica gel, 33% EtOAc in hexane) to give *trans*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexyl}-carbamic acid benzyl ester (1.20 g, 38%) as a pale yellow solid.

ESI MS m/e 434, $M + H^+$; ^1H NMR (300 MHz, CDCl_3) δ 7.76-7.82 (m, 1 H), 7.40-7.50 (m, 2 H), 7.25-7.40 (m, 5 H), 6.95-7.04 (m, 1 H), 5.08 (s, 2 H), 4.82-5.05 (m, 1 H), 4.40-4.70 (m, 1 H), 3.40-3.60 (m, 1 H), 3.35 (t, 2 H, $J = 6.3$ Hz), 3.26 (s, 6 H), 1.96-2.18 (m, 2 H), 1.80-1.96 (m, 2 H), 1.45-1.61 (m, 1 H), 1.00-1.20 (m, 4 H).

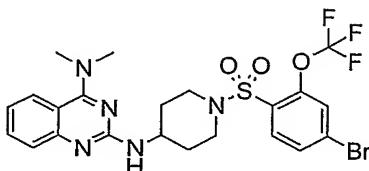
Step D: Synthesis of *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexyl}-2-trifluoromethoxy-benzenesulfonamide.

To a suspension of *trans*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexyl}-carbamic acid benzyl ester (500 mg, 1.15 mmol) in MeOH (5 mL) was added 5% Pd/C (50 mg). The mixture was stirred at ambient temperature under hydrogen atmosphere for 2 hr, at 50 °C for 8 hr, and at ambient temperature for 10.5 hr, filtered, and concentrated to give a colorless oil. To a solution of the above oil in CH_2Cl_2 (5 mL) was added diisopropylethylamine (420 μL , 2.41 mmol). The mixture was cooled to 4 °C and a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (431 mg, 1.27 mmol) in CH_2Cl_2 (2 mL) was added below 5 °C. The reaction mixture was stirred at 4 °C for 1.5 hr. The reaction was quenched with saturated aqueous NaHCO_3 . The aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by flash chromatography (NH-silica gel, 33% to 50% EtOAc in hexane) to give *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexyl}-2-trifluoromethoxy-benzenesulfonamide (560 mg, 81%) as a pale yellow solid.

ESI MS m/e 602, $M + H^+$; ^1H NMR (300 MHz, CDCl_3) δ 7.90 (d, 1 H, $J = 8.9$ Hz), 7.80

(dd, 1 H, $J = 8.4, 0.9$ Hz), 7.38-7.58 (m, 4 H), 7.01 (ddd, 1 H, $J = 8.4, 6.7, 1.6$ Hz), 4.85-5.04 (m, 1 H), 3.31 (t, 2 H, $J = 6.3$ Hz), 3.24 (s, 6 H), 3.07-3.20 (m, 1 H), 1.70-1.90 (m, 4 H), 1.42-1.58 (m, 1 H), 0.90-1.28 (m, 4 H).

Example 4



*N*²-[1-(4-Bromo-2-trifluoromethoxy-benzenesulfonyl)-piperidin-4-yl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine

Step A: Synthesis of *N*²-(1-benzyl-piperidin-4-yl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine.

Using the procedure for the step G of example 1, the title compound was obtained. ESI MS m/e 362, $M + H^+$; ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, $J = 7.6$ Hz, 1 H), 7.20-7.52 (m, 7 H), 6.97-7.05 (m, 1 H), 4.74-4.90 (m, 1 H), 3.90-4.05 (m, 1 H), 3.53 (s, 2 H), 3.26 (s, 6 H), 2.78-2.90 (m, 2 H), 2.02-2.24 (m, 4 H), 1.48-1.62 (m, 2 H).

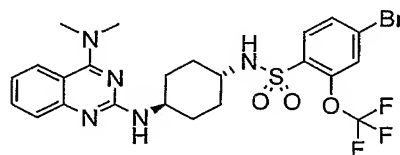
Step B: Synthesis of *N*²-[1-(4-bromo-2-trifluoromethoxy-benzenesulfonyl)-piperidin-4-yl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine.

To a solution of *N*²-(1-benzyl-piperidin-4-yl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine (500 mg, 1.38 mmol) in MeOH (5 mL) was added 20% Pd(OH)₂ (100 mg). The mixture was stirred at ambient temperature under hydrogen atmosphere for 1.5 hr, at 50 °C for 8 hr, at ambient temperature for 16.5 hr, filtered through a pad of celite, and concentrated. To a solution of the residue in CH₂Cl₂ (5 mL) was added diisopropylethylamine (510 μ L, 2.93 mmol). The mixture was cooled to 4 °C and a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (493 mg, 1.45 mmol) in CH₂Cl₂ (2 mL) was added below 5 °C. The reaction mixture was stirred at 4 °C for 2 hr. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄,

filtered, concentrated, and purified by flash chromatography (NH-silica gel, 33% EtOAc in hexane) to give *N*²-[1-(4-bromo-2-trifluoromethoxy-benzenesulfonyl)-piperidin-4-yl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine (339 mg, 43%) as a pale yellow solid.

ESI MS *m/e* 596, *M* + *Na*⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.87 (d, *J* = 8.2 Hz, 1 H), 7.81 (dd, *J* = 8.3, 1.0 Hz, 1 H), 7.36-7.61 (m, 4 H), 7.04 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1 H), 4.77 (d, *J* = 7.8 Hz, 1 H), 3.97-4.14 (m, 1 H), 3.68-3.86 (m, 2 H), 3.25 (s, 6 H), 2.87-3.01 (m, 2 H), 2.10-2.23 (m, 2 H), 1.51-1.70 (m, 2 H).

Example 5



***trans*-4-Bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzenesulfonamide**

Step A: Synthesis of *trans*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester.

To a solution of *trans*-cyclohexane-1,4-diamine (15.0 g, 131 mmol) in 1,4-dioxane (85 mL) was added (Boc)₂O (3.61 g, 16.5 mmol) dropwise over 4 hr. The mixture was stirred at ambient temperature for 19 hr and concentrated. To the residue was added H₂O and the insoluble material was removed by filtration. The filtrate was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated to give *trans*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester (3.15 g, 11% based on diamine, 89% based on (Boc)₂O) as a white solid.

ESI MS *m/e* 215, *M* + *H*⁺; ¹H NMR (300 MHz, CDCl₃) δ 4.43 (brs, 1 H), 3.36 (brs, 1 H), 2.57-2.70 (m, 1 H), 1.78-2.04 (m, 4 H), 1.44 (s, 9 H), 1.05-1.38 (m, 4 H).

Step B: Synthesis of *trans*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester.

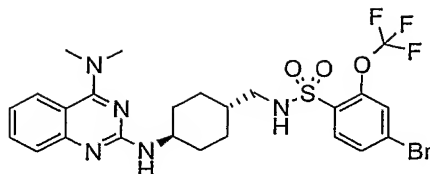
Using the procedure for the step G of example 1, the title compound was obtained. ESI MS *m/e* 408, *M* + *Na*⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, *J* = 8.2 Hz, 1 H), 7.39-

7.52 (m, 2 H), 7.02 (ddd, 1 H, $J = 8.3, 6.3, 1.9$ Hz, 1 H), 4.68-4.78 (m, 1 H), 4.43 (brs, 1 H), 3.89 (brs, 1 H), 3.46 (brs, 1 H), 3.25 (s, 6 H), 2.15-2.24 (m, 2 H), 1.97-2.10 (m, 2 H), 1.45 (s, 9 H), 1.21-1.35 (m, 4 H).

Step C: Synthesis of *trans*-4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzenesulfonamide.

To a solution of *trans*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (500 mg, 1.30 mmol) in EtOAc (5 mL) was added 4 M hydrogen chloride in EtOAc (5 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated to give a white solid. To a suspension of the above solid in CH₂Cl₂ (7 mL) was added diisopropylethylamine (905 μ L, 5.20 mmol). The mixture was cooled to 4 °C and a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (462 mg, 1.36 mmol) in CH₂Cl₂ (2 mL) was added below 5 °C. The reaction mixture was stirred at 4 °C for 1.5 hr. To the reaction mixture was added a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (88 mg, 0.26 mmol) in CH₂Cl₂ (0.5 mL) and the mixture was stirred at 4 °C for 1 hr. To the reaction mixture was added diisopropylethylamine (230 μ L, 1.32 mmol) and the mixture was stirred at 4 °C for 1.5 hr. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 50% EtOAc in hexane) to give *trans*-4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzenesulfonamid (339 mg, 44%) as a white solid.

ESI MS m/e 588, $M + H^+$; ¹H NMR (300 MHz, CDCl₃) δ 7.92 (d, $J = 8.9$ Hz, 1 H), 7.80 (dd, $J = 8.3, 0.7$ Hz, 1 H), 7.37-7.59 (m, 4 H), 6.99-7.06 (m, 1 H), 4.64-4.75 (m, 1 H), 3.78-3.94 (m, 1 H), 3.17-3.30 (m, 7 H), 2.09-2.20 (m, 2 H), 1.85-1.97 (m, 2 H), 1.12-1.47 (m, 4 H).

Example 6

***trans*-4-Bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzenesulfonamide**

Step A: Synthesis of *trans*-(4-amino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester.

To a suspension of *trans*-[4-(*tert*-butoxycarbonylamino-methyl)-cyclohexyl]-carbamic acid benzyl ester (4.00 g, 11.0 mmol) in MeOH (40 mL) was added 5% Pd/C (400 mg). The mixture was stirred at ambient temperature under hydrogen atmosphere for 1 hr, filtered through a pad of celite, and concentrated to give a white solid. A suspension of the above solid in hexane (15 mL) was stirred at ambient temperature for 30 min. The solid was collected by filtration, washed with hexane, dried under reduced pressure to give *trans*-(4-amino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (2.52 g, 100%) as a white solid.

ESI MS *m/e* 229, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 4.56-4.88 (m, 1 H), 3.00 (t, $J = 6.5$ Hz, 2 H), 2.54-2.65 (m, 1 H), 1.70-1.94 (m, 4 H), 1.44 (s, 9 H), 1.18-1.50 (m, 1 H), 0.92-1.15 (m, 4 H).

Step B: Synthesis of *trans*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester.

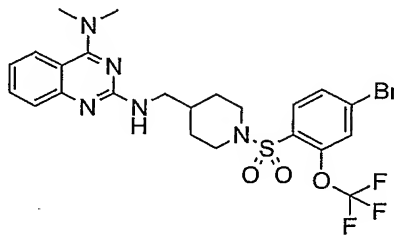
Using the procedure for the step G of example 1, the title compound was obtained. ESI MS *m/e* 422, $M + Na^+$; 1H NMR (300 MHz, $CDCl_3$) 7.81 (d, $J = 7.9$ Hz, 1 H), 7.38-7.52 (m, 2 H), 6.96-7.07 (m, 1 H), 4.55-4.84 (m, 2 H), 3.75-3.97 (m, 1 H), 3.26 (s, 6 H), 3.01 (t, $J = 6.4$ Hz, 2 H), 2.15-2.30 (m, 2 H), 1.75-1.88 (m, 2 H), 1.45 (s, 9 H), 1.35-1.54 (m, 1 H), 1.00-1.30 (m, 4 H).

Step C: Synthesis of *trans*-4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzenesulfonamide.

To a suspension of *trans*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester (500 mg, 1.25 mmol) in EtOAc (5 mL) was added 4 M hydrogen chloride in EtOAc (5 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated to give a white solid. To a suspension of the above solid in CH₂Cl₂ (7 mL) was added diisopropylethylamine (905 μ L, 5.20 mmol). The mixture was cooled to 4 °C and a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (446 mg, 1.31 mmol) in CH₂Cl₂ (2 mL) was added below 5 °C. The reaction mixture was stirred at 4 °C for 1.5 hr. To the reaction mixture was added a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (85mg, 0.25 mmol) in CH₂Cl₂ (0.5 mL) and the mixture was stirred at 4 °C for 1 hr. To the reaction mixture was added diisopropylethylamine (220 μ L, 1.26 mmol) and the mixture was stirred at 4 °C for 1 hr. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 50% EtOAc in hexane) to give *trans*-4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzenesulfonamide (624 mg, 83%) as a pale yellow solid.

ESI MS *m/e* 602, *M* + *H*⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.89 (d, *J* = 8.9 Hz, 1 H), 7.80 (d, *J* = 8.5 Hz, 1 H), 7.39-7.60 (m, 4 H), 7.04 (ddd, *J* = 8.2, 6.8, 1.6 Hz, 1 H), 3.71-3.92 (m, 1 H), 3.30 (s, 6 H), 2.85 (d, *J* = 6.5 Hz, 2 H), 2.10-2.22 (m, 2 H), 1.70-1.86 (m, 2 H), 1.37-1.53 (m, 1 H), 0.98-1.32 (m, 4 H).

Example 7



***N*²-[1-(4-Bromo-2-trifluoromethoxy-benzenesulfonyl)-piperidin-4-ylmethyl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine**

Step A: Synthesis of 4-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester.

To a solution of *C*-piperidin-4-yl-methylamine (15.0 g, 131 mmol) in toluene (165 mL) was added benzaldehyde (13.9 g, 131 mmol) and the mixture was stirred at reflux with a Dean-Stark trap under N₂ atmosphere for 3 hr, and cooled on an ice-bath. To the reaction mixture was added (Boc)₂O (31.5 g, 144 mmol) dropwise over 15 min. The mixture was stirred at ambient temperature for 2.5 days, and concentrated. To the residue was added 1 M aqueous KHSO₄ and the mixture was stirred at ambient temperature for 7 hr, the aqueous layer was washed with Et₂O (twice), alkalized with sodium hydroxide, and extracted with CHCl₃ (five times). The combined organic layer was dried over MgSO₄, filtered, concentrated. The precipitate was suspended in hexane (10 mL) and the suspension was stirred at ambient temperature for 10 min. The solid was collected by filtration and dried under reduced pressure to give 4-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (25.8 g, 92%) as a white solid.

ESI MS *m/e* 215, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 3.85-4.22 (m, 2 H), 2.90 (d, *J* = 6.8 Hz, 2 H), 2.50-2.80 (m, 2 H), 1.70-2.02 (m, 3 H), 1.45 (s, 9 H), 1.10-1.28 (m, 2 H).

Step B: Synthesis of 4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester.

Using the procedure for the step G of example 1, the title compound was obtained. ESI MS *m/e* 386, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (d, *J* = 8.4 Hz, 1 H), 7.41-7.53 (m, 2 H), 6.99-7.06 (m, 1 H), 5.16 (brs, 1 H), 4.00-4.20 (m, 2 H), 3.41 (t, *J* = 6.1 Hz, 2 H), 3.26 (s, 6 H), 2.60-2.77 (m, 2 H), 1.67-1.84 (m, 3 H), 1.45 (s, 9 H), 1.11-1.28 (m, 2 H).

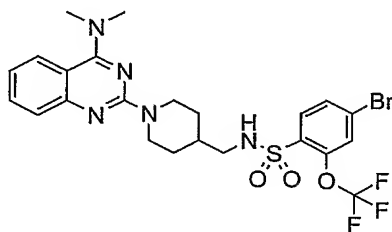
Step C: Synthesis of *N*²-[1-(4-bromo-2-trifluoromethoxy-benzenesulfonyl)-piperidin-4-ylmethyl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine.

To a suspension of 4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester (500 mg, 1.30 mmol) in EtOAc (5 mL) was added 4 M hydrogen chloride in EtOAc (5 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated to give a white solid. To a suspension of the above solid in CH₂Cl₂ (5 mL) was added diisopropylethylamine (480 μL, 2.76 mmol). The mixture was cooled to 4 °C and a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (462 mg, 1.36 mmol) in CH₂Cl₂ (2 mL) was added below 5 °C. The reaction

mixture was stirred at 4 °C for 3 hr. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 14% to 20% EtOAc in hexane) to give *N*²-[1-(4-bromo-2-trifluoromethoxy-benzenesulfonyl)-piperidin-4-ylmethyl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine (420 mg, 55%) as a yellow solid.

ESI MS *m/e* 588, *M* + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.85 (d, *J* = 8.9 Hz, 1 H), 7.81 (dd, *J* = 8.7, 0.9 Hz, 1 H), 7.40-7.56 (m, 4 H), 7.04 (ddd, *J* = 8.2, 6.7, 1.6 Hz, 1 H), 5.10-5.46 (brs, 1 H), 3.85 (d, *J* = 12.4 Hz, 2 H), 3.40 (t, *J* = 6.4 Hz, 2 H), 3.27 (s, 6 H), 2.56-2.67 (m, 2 H), 1.64-1.91 (m, 3 H), 1.23-1.43 (m, 2 H).

Example 8



4-Bromo-*N*-[1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-ylmethyl]-2-trifluoromethoxy-benzenesulfonamide

Step A: Synthesis of 4-(benzyloxycarbonylamino-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

To a solution of 4-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (7.00 g, 32.7 mmol) in CHCl₃ (70 mL) was added triethylamine (3.64 g, 36.0 mmol). The resulting solution was cooled to 4 °C and ZCl (6.13 g, 35.9 mmol) was added below 8 °C over 15 min. The reaction mixture was stirred at ambient temperature for 18 hr, and poured into saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times), dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (silica gel, 33% to 50% EtOAc in hexane) to give 4-(benzyloxycarbonylamino-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (10.7 g, 94%) as a colorless oil.

ESI MS *m/e* 371, *M* + Na⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.26-7.37 (m, 5 H), 5.09 (s, 2 H), 4.84-5.01 (m, 1 H), 3.95-4.22 (m, 2 H), 2.98-3.16 (m, 2 H), 2.66 (t, *J* = 12.4 Hz, 2 H),

1.58-1.72 (m, 3 H), 1.45 (s, 9 H), 0.98-1.18 (m, 2 H).

Step B: Synthesis of piperidin-4-ylmethyl-carbamic acid benzyl ester hydrochloride.

A solution of 4-(benzyloxycarbonylamino-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (10.2 g, 29.3 mmol) in EtOAc (100 mL) was cooled on an ice-bath and 4 M hydrogen chloride in EtOAc (100 mL) was added. The mixture was stirred at ambient temperature for 1 hr and concentrated. The residue was suspended in hexane (30 mL) and the mixture was stirred at ambient temperature for 30 min. The solid was collected by filtration, washed with hexane, and dried under reduced pressure to give piperidin-4-ylmethyl-carbamic acid benzyl ester hydrochloride (7.24 g, 87%) as a white solid.

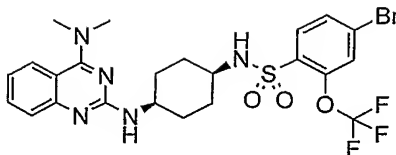
ESI MS *m/e* 271, M (free) + Na⁺; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.10 (brs, 2 H), 7.20-7.50 (m, 6 H), 5.02 (s, 2 H), 3.15-3.28 (m, 2 H), 2.68-3.02 (m, 4 H), 1.56-1.82 (m, 3 H), 1.20-1.52 (m, 2 H).

Step C: Synthesis of [1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-ylmethyl]-carbamic acid benzyl ester.

Using the procedure for the step C of example 3, the title compound was obtained. ESI MS *m/e* 420, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, *J* = 8.2 Hz, 1 H), 7.21-7.49 (m, 7 H), 6.95-7.04 (m, 1 H), 5.06-5.17 (m, 2 H), 4.83-4.98 (m, 3 H), 3.24 (s, 6 H), 3.00-3.16 (m, 2 H), 2.77-2.91 (m, 2 H), 1.58-1.97 (m, 3 H), 1.12-1.33 (m, 2 H).

Step D: Synthesis of 4-bromo-*N*-[1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-ylmethyl]-2-trifluoromethoxy-benzenesulfonamide.

Using the procedure for the step D of example 3, the title compound was obtained. ESI MS *m/e* 588, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.87 (d, *J* = 8.7 Hz, 1 H), 7.78 (d, *J* = 8.2 Hz, 1 H), 7.44-7.59 (m, 4 H), 6.97-7.06 (m, 1 H), 4.94-5.04 (m, 1 H), 4.89 (d, *J* = 13.2 Hz, 2 H), 3.25 (s, 6 H), 2.75-2.88 (m, 4 H), 1.64-1.82 (m, 3 H), 1.05-1.28 (m, 2 H).

Example 9***cis*-4-Bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzenesulfonamide****Step A: Synthesis of *cis*-(4-benzyloxycarbonylamino-cyclohexyl)-carbamic acid benzyl ester.**

To a suspension of *cis*-cyclohexane-1,4-dicarboxylic acid (25.0 g, 145 mmol) in benzene (125 mL) were added phosphorazidic acid diphenyl ester (81.9 g, 298 mmol) and triethylamine (30.1 g, 297 mmol). The reaction mixture was stirred at reflux for 2.5 hr (**Caution! Vigorous exothermic reaction**). Benzyl alcohol (32.2 g, 298 mmol) was added and the mixture was stirred at reflux for 24 hr. The reaction mixture was concentrated and the residue was dissolved in EtOAc and H₂O. The organic layer was separated and the aqueous layer was extracted with EtOAc (twice). The combined organic layer was washed with 1 M aqueous KHSO₄, saturated aqueous NaHCO₃, and brine, dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (silica gel, 33% EtOAc in hexane) to give *cis*-(4-benzyloxycarbonylamino-cyclohexyl)-carbamic acid benzyl ester (52.0 g, 94%) as a colorless oil.

ESI MS *m/e* 405, *M* + Na⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.15-7.40 (m, 10 H), 5.07 (s, 4 H), 4.70-5.00 (m, 2 H), 3.52-3.80 (m, 2 H), 1.60-1.80 (m, 4 H), 1.45-1.60 (m, 4 H).

Step B: Synthesis of *cis*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester.

To a solution of *cis*-(4-benzyloxycarbonylamino-cyclohexyl)-carbamic acid benzyl ester (91.7 g, 240 mmol) in MeOH (460 mL) was added 5% Pd/C (9.17 g). The reaction mixture was stirred at ambient temperature under hydrogen atmosphere for 2.5 days, filtered through a pad of celite, and concentrated to give a diamine as a colorless oil. To a solution of the diamine in MeOH (550 mL) was added a solution of (Boc)₂O (6.59 g, 30.2 mmol) in MeOH (80 mL) dropwise over 4 hr. The reaction mixture was stirred at

ambient temperature for 1.5 days and concentrated. After dissolution with H₂O, the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, and concentrated to give *cis*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester (7.78 g, 15%, crude) as a colorless oil. The aqueous layer was concentrated and the residue was dissolved in MeOH, dried over MgSO₄, filtered, and concentrated to give a recovered diamine (32.9 g) as a colorless oil. To a solution of the recovered diamine (32.9 g, 288 mmol) in MeOH (660 mL) was added a solution of (Boc)₂O (6.29 g, 28.8 mmol) in MeOH (80 mL) dropwise over 5 hr. The reaction mixture was stirred at ambient temperature for 10 hr and concentrated. After dissolution with H₂O, the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, and concentrated to give *cis*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester (8.16 g, 16%, crude) as a colorless oil. The aqueous layer was concentrated and the residue was dissolved in MeOH, dried over MgSO₄, filtered, and concentrated to give a recovered diamine (23.1 g) as a colorless oil. To a solution of the recovered diamine (23.1 g, 202 mmol) in MeOH (462 mL) was added a solution of (Boc)₂O (4.42 g, 20.3 mmol) in MeOH (56 mL) dropwise over 4 hr. The reaction mixture was stirred at ambient temperature for 3.5 days and concentrated. After dissolution with H₂O, the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, and concentrated to give *cis*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester (5.01 g, 10% based on starting material) as a colorless oil. The aqueous layer was concentrated and the residue was dissolved in MeOH, dried over MgSO₄, filtered, and concentrated to give a recovered diamine (16.0 g) as a colorless oil. To a solution of the recovered diamine (16.0 g, 140 mmol) in MeOH (320 mL) was added a solution of (Boc)₂O (3.06 g, 14.0 mmol) in MeOH (40 mL) dropwise over 4 hr. The reaction mixture was stirred at ambient temperature for 13 hr and concentrated. After dissolution with H₂O, the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, and concentrated to give *cis*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester (3.53 g, 7% based on the starting material) as a colorless oil. The aqueous layer was concentrated and the residue was dissolved in MeOH, dried over MgSO₄, filtered, and concentrated to give a recovered diamine (11.1 g) as a colorless oil.

ESI MS *m/e* 215, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 4.30-4.82 (m, 1 H), 3.50-3.80 (m, 1 H), 2.78-2.95 (m, 1 H), 1.44 (s, 9H), 1.20-1.80 (m, 8 H).

Step C: Synthesis of *cis*-*N*²-(4-amino-cyclohexyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine.

A mixture of (2-chloro-quinazolin-4-yl)-dimethyl-amine obtained in step B of example 1 (3.00 g, 14.4 mmol) and *cis*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester (3.72 g, 17.4 mmol) in 2-propanol (10 mL) was stirred at reflux for 5.5 days, poured into saturated aqueous NaHCO₃, and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica, 20% EtOAc in hexane) to give *cis*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester including solvent (5.44 g) as a colorless oil. To a solution of the above material (5.44 g) in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (50 mL). The reaction mixture was stirred at ambient temperature for 2 hr, and concentrated. The residue was alkalized with saturated aqueous NaHCO₃, and the precipitate was collected by filtration to give *cis*-*N*²-(4-amino-cyclohexyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine (2.26 g, 55%) as a white solid. The aqueous layer was extracted CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, and concentrated to give *cis*-*N*²-(4-amino-cyclohexyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine (687 mg, 17%) as a white solid.

ESI MS *m/e* 285, M⁺; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.86 (d, *J* = 7.5 Hz, 1 H), 7.47 (t, *J* = 8.3 Hz, 1 H), 7.29 (d, *J* = 8.3 Hz, 1 H), 7.01 (t, *J* = 7.6 Hz, 1 H), 6.56 (d, *J* = 7.5 Hz, 1 H), 3.83-4.06 (m, 1 H), 3.38-3.52 (m, 1 H), 3.20 (s, 6 H), 1.22-1.82 (m, 8 H).

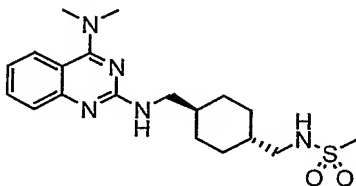
Step D: Synthesis of *cis*-4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzenesulfonamide.

To a suspension of *cis*-*N*²-(4-amino-cyclohexyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine (680 mg, 2.38 mmol) in CH₂Cl₂ (7 mL) was added diisopropylethylamine (620 μL, 3.56 mmol). The mixture was cooled on an ice-bath and a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (849 mg, 2.50 mmol) in CH₂Cl₂ (3 mL) was added dropwise. The reaction mixture was stirred on an ice-bath for 6.5 hr. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 33% EtOAc in hexane) to give *cis*-4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-

trifluoromethoxy-benzenesulfonamide (782 mg, 56%) as a pale yellow solid.

ESI MS m/e 588, M^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, $J = 8.9$ Hz, 1 H), 7.81 (dd, $J = 8.3, 1.2$ Hz, 1 H), 7.41-7.58 (m, 4 H), 7.04 (ddd, $J = 8.3, 6.6, 1.6$ Hz, 1 H), 4.00-4.12 (m, 1 H), 3.36-3.45 (m, 1 H), 3.31 (s, 6 H), 1.54-1.84 (m, 8 H).

Example 10

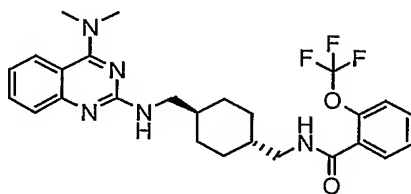


***trans*-N-{4-[(4-Dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-methanesulfonamide**

Step A: Synthesis of *trans*-N-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-methane sulfonamide.

Using the procedure for the step H of example 1, the title compound was obtained. ESI MS m/e 392, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, $J = 7.8$ Hz, 1 H), 7.38-7.53 (m, 2 H), 7.02 (ddd, $J = 8.3, 6.6, 1.6$ Hz, 1 H), 5.07 (brs, 1 H), 4.61 (brs, 1 H), 3.36 (t, $J = 6.2$ Hz, 2 H), 3.27 (s, 6 H), 2.94 (s, 3 H), 2.91-3.01 (m, 2 H), 1.76-1.98 (m, 4 H), 1.37-1.64 (m, 2 H), 0.85-1.12 (m, 4 H).

Example 11



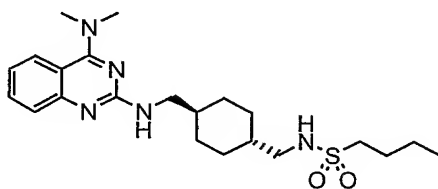
***trans*-N-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzamide**

Step A: Synthesis of *trans*-N-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-

cyclohexylmethyl}-2-trifluoromethoxy-benzamide.

To a suspension of *trans*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]cyclohexylmethyl}-carbamic acid *tert*-butyl ester obtained in step G of example 1 (800 mg, 1.93 mmol) in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (10 mL). The mixture was stirred at ambient temperature for 60 min and concentrated to give a white solid. To a suspension of the solid in CH₂Cl₂ (10 mL) was added diisopropylethylamine (706 μ L, 4.05 mmol). The mixture was cooled at 4 °C and a solution of 2-(trifluoromethoxy)benzoyl chloride (455 mg, 2.03 mmol) in CH₂Cl₂ (4 mL) was added below 5 °C. The reaction mixture was stirred at 4 °C for 90 min. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 33% EtOAc in hexane) to give *trans*-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzamide (772 mg, 80%) as a pale yellow solid.

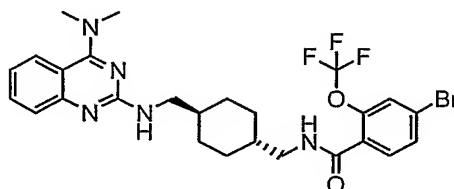
ESI MS *m/e* 502, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.90 (dd, *J* = 7.4, 1.6, Hz, 1 H), 7.81 (d, *J* = 8.1 Hz, 1 H), 7.33-7.55 (m, 4 H), 7.29 (d, *J* = 8.8, Hz, 1 H), 6.96-7.08 (m, 1 H), 6.55 (brs, 1 H), 4.97 (brs, 1 H), 3.28-3.43 (m, 4 H), 3.26 (s, 6 H), 1.76-2.10 (m, 4 H), 1.44-1.72 (m, 2 H), 0.90-1.21 (m, 4 H).

Example 12***trans*-Butane-1-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide****Step A: Synthesis of *trans*-butane-1-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.**

Using the procedure for the step H of example 1, the title compound was obtained. ESI MS *m/e* 434, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (d, *J* = 8.2 Hz, 1 H), 7.35-

7.54 (m, 2 H), 6.97-7.07 (m, 1 H), 4.41 (t, $J = 6.1$ Hz, 1 H), 3.36 (t, $J = 6.1$ Hz, 2 H), 3.27 (s, 6 H), 2.89-3.05 (m, 4 H), 1.71-1.97 (m, 6 H), 1.37-1.65 (m, 4 H), 0.82-1.12 (m, 7 H).

Example 13



***trans*-4-Bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzamide**

Step A: Synthesis of 4-bromo-2-trifluoromethoxy-benzaldehyde.

A solution of 4-bromo-1-iodo-2-trifluoromethoxy-benzene (1.00 g, 2.72 mmol) in THF (15 mL) was cooled to -78 °C, and 2.66 M BuLi in hexane (2.05 mL, 5.44 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1.5 h, and *N*-formylmorpholine (0.57 mL, 5.63 mmol) was added. The reaction mixture was stirred at -78 °C for 15 min and at ambient temperature for 80 min. The reaction was quenched with 0.25 M aqueous citric acid (10 mL), and the resulting mixture was extracted with EtOAc (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by flash chromatography (silica gel, 2% to 5% EtOAc in hexane) to give 4-bromo-2-trifluoromethoxy-benzaldehyde (560 mg, 77%) as a pale brown solid.

CI MS m/e 269, $M + H^+$; ^1H NMR (300 MHz, CDCl_3) δ 10.33 (s, 1 H), 7.85 (d, $J = 8.1$ Hz, 1 H), 7.50-7.67 (m, 2 H).

Srep B: Synthesis of 4-bromo-2-trifluoromethoxy-benzoic acid.

A solution of 4-bromo-2-trifluoromethoxy-benzaldehyde (550 mg, 2.04 mmol) in 1,4-dioxane (27 mL) and H_2O (9 mL) was cooled at 4 °C. To the solution were added amidosulfuric acid (296 mg, 3.05 mmol) and sodium dihydrogen phosphate dihydrate (1.4 g, 8.98 mmol). The mixture was stirred at 4 °C for 15 min. To the reaction mixture was added a solution of sodium chlorite (238 mg, 2.63 mmol) in H_2O (1.5 mL) and stirred at 4 °C for 15 min. To the reaction mixture was added Na_2CO_3 (304 mg, 2.41 mmol) and stirred

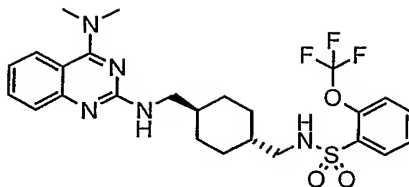
at 4 °C for 15 min. The mixture was acidified with conc-HCl (pH = 1), and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (silica gel, 1% MeOH in CHCl₃) to give 4-bromo-2-trifluoromethoxy-benzoic acid (471 mg, 81%) as a white solid.

ESI MS m/e 284, M⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.98 (d, *J* = 8.4 Hz, 1 H), 7.53-7.62 (m, 2 H).

Step C: Synthesis of *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzamide.

To a solution of 4-bromo-2-trifluoromethoxy-benzoic acid (454 mg, 1.59 mmol) in CH₂Cl₂ (6 mL) were added DMF (1.5 μL, 0.02 mmol) and SOCl₂ (158 μL, 2.17 mmol). The mixture was stirred at reflux for 1 hr and concentrated to give acid chloride as a pale yellow oil. To a suspension of *trans*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]cyclohexylmethyl}-carbamic acid *tert*-butyl ester obtained in step G of example 1 (624 mg, 1.51 mmol) in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (8 mL). The mixture was stirred at ambient temperature for 40 min and concentrated to give a white solid. To a suspension of the solid in CH₂Cl₂ (6 mL) was added diisopropylethylamine (552 μL, 3.17 mmol). The mixture was cooled at 4 °C and a solution of acid chloride in CH₂Cl₂ (6 mL) was added below 5 °C. The reaction mixture was stirred at 4 °C for 2.5 hr. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 33% EtOAc in hexane) to give *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzamide (309 mg, 35%) as a pale yellow solid.

ESI MS m/e 580, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.89 (d, *J* = 8.4 Hz, 1 H), 7.81 (d, *J* = 8.2 Hz, 1 H), 7.39-7.67 (m, 4 H), 7.02 (ddd, *J* = 8.2, 6.4, 1.9 Hz, 1 H), 6.53 (brs, 1 H), 4.99 (brs, 1 H), 3.37 (t, *J* = 6.5 Hz, 2 H), 3.32 (t, *J* = 6.3 Hz, 2 H), 3.27 (s, 6 H), 1.76-2.02 (m, 4 H), 1.48-1.67 (m, 2 H), 0.94-1.16 (m, 4 H).

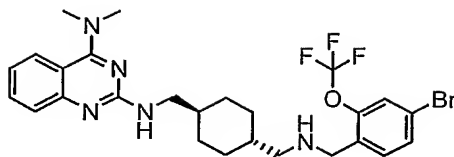
Example 14

***trans*-N-{4-[(4-Dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide.**

Step A: Synthesis of *trans*-N-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide.

To a suspension of *trans*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]cyclohexylmethyl}-carbamic acid *tert*-butyl ester obtained in step G of example 1 (500 mg, 1.21 mmol) in EtOAc (8 mL) was added 4 M hydrogen chloride in EtOAc (7 mL). The mixture was stirred at ambient temperature for 40 min and concentrated to give a white solid. To a suspension of the solid in CH₂Cl₂ (7 mL) was added pyridine (215 μ L, 2.66 mmol). The mixture was cooled at 4 °C and a solution of 2-trifluoromethoxy-benzenesulfonyl chloride (331 mg, 1.27 mmol) in CH₂Cl₂ (2 mL) was added below 5 °C. The reaction mixture was stirred at 4 °C for 2 hr. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 20% EtOAc in hexane) to give *trans*-N-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide (231 mg, 36%) as a pale yellow solid.

ESI MS *m/e* 538, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 8.03 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.81 (d, *J* = 8.2 Hz, 1 H), 7.57-7.66 (m, 1 H), 7.36-7.52 (m, 4 H), 7.02 (ddd, *J* = 8.3, 6.5, 1.7 Hz, 1 H), 4.94 (brs, 1 H), 4.66 (brs, 1 H), 3.34 (t, *J* = 6.4 Hz, 2 H), 3.26 (s, 6 H), 2.78 (t, *J* = 6.2 Hz, 2 H), 1.68-2.01 (m, 4 H), 1.29-1.60 (m, 2 H), 0.79-1.07 (m, 4 H).

Example 15

***trans*- N^2 -{4-[(4-Bromo-2-trifluoromethoxy-benzylamino)-methyl]-cyclohexylmethyl}- N^4,N^4 -dimethyl-quinazoline-2,4-diamine**

Step A: Synthesis of *trans*- N^2 -(4-aminomethyl-cyclohexylmethyl)- N^4,N^4 -dimethyl-quinazoline-2,4-diamine.

To a suspension of *trans*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester (20.1 g, 48.6 mmol) in EtOAc (200 mL) was added 4 M hydrogen chloride in EtOAc (200 mL). The mixture was stirred at ambient temperature for 90 min and concentrated to give a solid. The solid was alkalized with saturated aqueous NaHCO_3 (pH = 9), concentrated, and purified by flash chromatography (NH silica gel, 33% MeOH in CHCl_3) to give *trans*- N^2 -(4-aminomethyl-cyclohexylmethyl)- N^4,N^4 -dimethyl-quinazoline-2,4-diamine (14.7 g, 97%) as a white solid. ESI MS m/e 314, $M + H^+$; ^1H NMR (300 MHz, CDCl_3) δ 7.81 (d, $J = 8.2$ Hz, 1 H), 7.42-7.52 (m, 2 H), 7.01 (ddd, $J = 8.2, 6.2, 0.9$ Hz, 1 H), 4.95 (brs, 1 H), 3.36 (t, $J = 6.3$ Hz, 2 H), 3.26 (s, 6 H), 2.52 (d, $J = 6.4$ Hz, 2 H), 1.75-1.96 (m, 5 H), 1.48-1.66 (m, 1 H), 0.82-1.40 (m, 6 H).

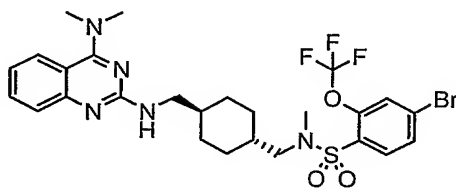
Step B: Synthesis of *trans*- N^2 -{4-[(4-bromo-2-trifluoromethoxy-benzylamino)-methyl]-cyclohexylmethyl}- N^4,N^4 -dimethyl-quinazoline-2,4-diamine.

To a solution of *trans*- N^2 -(4-aminomethyl-cyclohexylmethyl)- N^4,N^4 -dimethyl-quinazoline-2,4-diamine (500 mg, 1.59 mmol) in CH_2Cl_2 (5 mL) were added 4-bromo-2-trifluoromethoxy-benzaldehyde obtained in step A of example 13 (428 mg, 1.59 mmol), acetic acid (95 mg, 1.59 mmol), and $\text{NaBH}(\text{OAc})_3$ (505 mg, 2.38 mmol). The reaction mixture was stirred at ambient temperature for 4 hr. The reaction was quenched with saturated aqueous NaHCO_3 . The aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by

flash chromatography (NH-silica gel, 50% EtOAc in hexane) to give *trans*-*N*²-{4-[(4-bromo-2-trifluoromethoxy-benzylamino)-methyl]-cyclohexylmethyl}-*N*¹,*N*⁴-dimethyl-quinazoline-2,4-diamine (783 mg, 89%) as a pale yellow solid.

ESI MS *m/e* 566, *M* + *H*⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, *J* = 8.2 Hz, 1 H), 7.34-7.52 (m, 5 H), 7.01 (ddd, *J* = 8.3, 6.2, 2.0 Hz, 1 H), 5.00 (brs, 1 H), 3.77 (s, 2 H), 3.36 (t, *J* = 6.3 Hz, 2 H), 3.26 (s, 6 H), 2.43 (d, *J* = 6.7 Hz, 2 H), 1.76-1.95 (m, 4 H), 1.34-1.65 (m, 2 H), 0.83-1.12 (m, 4 H).

Example 16



***trans*-4-Bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-*N*-methyl-2-trifluoromethoxy-benzenesulfonamide**

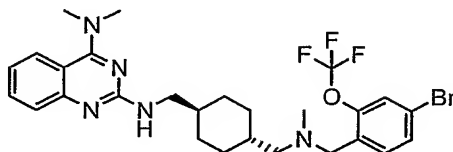
Step A: Synthesis of *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-*N*-methyl-2-trifluoromethoxy-benzenesulfonamide.

To a solution of *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide obtained in step H of example 1 (380 mg, 0.61 mmol) in DMF (2 mL) was added 60% sodium hydride in oil (24.6 mg, 0.61 mmol). The reaction mixture was stirred at ambient temperature for 80 min. The reaction mixture was cooled at 0 °C and iodomethane (38.3 μL, 0.61 mmol) was added and stirred at ambient temperature for 3 hr. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with EtOAc (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 25% EtOAc in hexane, and silica gel, 5% MeOH in CHCl₃) to give *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-*N*-methyl-2-trifluoromethoxy-benzenesulfonamide (268 mg, 69%) as a pale yellow solid.

ESI MS *m/e* 630, *M* + *H*⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.88 (d, *J* = 9.2 Hz, 1 H), 7.81 (d,

$J = 8.4$ Hz, 1 H), 7.41-7.57 (m, 4 H), 7.03 (ddd, $J = 8.4, 6.3, 1.8$ Hz, 1 H), 3.37 (t, $J = 6.2$ Hz, 2 H), 3.27 (s, 6 H), 2.97 (d, $J = 7.5$ Hz, 2H), 2.81 (s, 3H), 1.73-1.97 (m, 4H), 1.46-1.66 (m, 2H), 0.83-1.12 (m, 4H).

Example 17

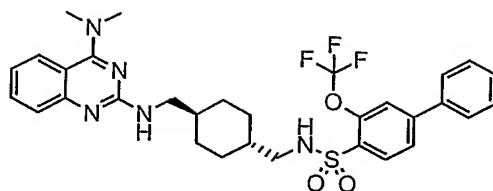


***trans*- N^2 -(4-[(4-bromo-2-trifluoromethoxy-benzyl)-methyl-amino]-methyl)-cyclohexylmethyl)- N^4,N^4 -dimethyl-quinazoline-2,4-diamine**

Step A: Synthesis of *trans*- N^2 -(4-[(4-bromo-2-trifluoromethoxy-benzyl)-methyl-amino]-methyl)-cyclohexylmethyl)- N^4,N^4 -dimethyl-quinazoline-2,4-diamine.

To a solution of *trans*- N^2 -(4-[(4-bromo-2-trifluoromethoxy-benzylamino)-methyl]-cyclohexylmethyl)- N^4,N^4 -dimethyl-quinazoline-2,4-diamine obtained in step B of example 15 (290 mg, 0.52 mmol) in CH_2Cl_2 (3 mL) were added 37% aqueous formaldehyde (42 mg, 0.52 mmol), acetic acid (31 mg, 0.52 mmol), and $\text{NaBH}(\text{OAc})_3$ (165 mg, 0.78 mmol). The reaction mixture was stirred at ambient temperature for 19 hr. The reaction was quenched with saturated aqueous NaHCO_3 . The aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by flash chromatography (NH-silica gel, 25% EtOAc in hexane) to give *trans*- N^2 -(4-[(4-bromo-2-trifluoromethoxy-benzyl)-methyl-amino]-methyl)-cyclohexylmethyl)- N^4,N^4 -dimethyl-quinazoline-2,4-diamine (153 mg, 51%) as a pale yellow solid.

ESI MS m/e 580, $\text{M} + \text{H}^+$; ^1H NMR (300 MHz, CDCl_3) δ 7.81 (d, $J = 7.6$ Hz, 1 H), 7.34-7.53 (m, 5 H), 7.02 (ddd, $J = 8.3, 6.2, 2.0$ Hz, 1 H), 3.44 (s, 2 H), 3.36 (t, $J = 6.3$ Hz, 2 H), 3.27 (s, 6 H), 2.14 (s, 3H), 2.11-2.18 (m, 2 H), 1.81-1.96 (m, 4H), 1.36-1.66 (m, 2 H), 0.73-1.13 (m, 4 H).

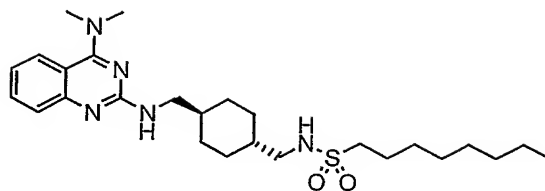
Example 18

***trans*- 3-Trifluoromethoxy-biphenyl-4-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide**

Step A: Synthesis of *trans*- 3-trifluoromethoxy-biphenyl-4-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

To a solution of *trans*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide obtained in step H of example 1 (122 mg, 0.198 mmol) in toluene (2.7 mL) were added MeOH (0.9 mL), 2 M aqueous K₂CO₃ (0.9 mL), phenylboronic acid (29.0 mg, 0.237 mmol), and tetrakis(triphenylphosphine)palladium (23.0 mg, 0.02 mmol). The reaction mixture was stirred at 130 °C for 10 hr. The mixture was poured into water, and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 25% EtOAc in hexane and silica gel, 9% MeOH in CHCl₃) to give *trans*-3-trifluoromethoxy-biphenyl-4-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide (77 mg, 0.125 mmol) as a white solid.

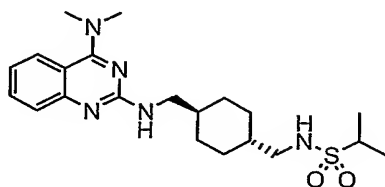
ESI MS *m/e* 614, *M* + H⁺; ¹H NMR (200 MHz, CDCl₃) δ 8.07 (d, *J* = 8.4 Hz, 1 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.38-7.67 (m, 9 H), 7.03 (ddd, *J* = 8.4, 6.2, 2.2 Hz, 1 H), 5.11 (brs, 1 H), 4.71 (brs, 1 H), 3.35 (t, *J* = 6.2 Hz, 2 H), 3.27 (s, 6 H), 2.73-2.90 (m, 2 H), 1.67-2.03 (m, 4 H), 1.30-1.64 (m, 2 H), 0.75-1.16 (m, 4 H).

Example 19

***trans*-Octane-1-sulfonic acid{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide**

Step A: Synthesis of *trans*-octane-1-sulfonic acid{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Using the procedure for the step H of example 1, the title compound was obtained. ESI MS m/e 490, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, $J = 7.8$ Hz, 1 H), 7.38-7.54 (m, 2 H), 7.02 (ddd, $J = 8.3, 6.6, 1.7$ Hz, 1 H), 5.01 (brs, 1 H), 4.45 (t, $J = 6.2$ Hz, 1 H), 3.36 (t, $J = 6.2$ Hz, 2 H), 3.26 (s, 6 H), 2.86-3.04 (m, 4 H), 1.70-1.96 (m, 6 H), 1.12-1.65 (m, 11 H), 0.76-1.11 (m, 8 H).

Example 20

***trans*-Propane-2-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide**

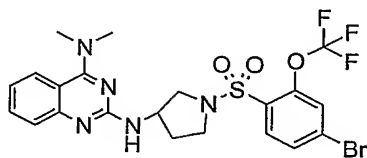
Step A: Synthesis of *trans*-propane-2-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

To a suspension of *trans*- N^2 -(4-aminomethyl-cyclohexylmethyl)- N^1, N^4 -dimethyl-quinazoline-2,4-diamine obtained in step A of example 15 (227 mg, 0.72 mmol) in CH_2Cl_2 (4 mL) was added diisopropylethylamine (263 μ L, 1.51 mmol). The mixture was cooled at 4 $^\circ$ C and a solution of 2-propanesulfonyl chloride (108 mg, 0.76 mmol) in CH_2Cl_2 (1 mL)

was added below 5 °C. The reaction mixture was stirred at ambient temperature for 12 hr. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 66% EtOAc in hexane) to give *trans*-propane-2-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide (135 mg, 45%) as a pale yellow solid.

ESI MS *m/e* 420, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (d, *J* = 7.8 Hz, 1 H), 7.39-7.52 (m, 2 H), 7.02 (ddd, *J* = 8.3, 6.5, 1.7 Hz, 1 H), 5.02 (brs, 1 H), 4.22 (t, *J* = 6.2 Hz, 1 H), 3.36 (t, *J* = 6.2 Hz, 2 H), 3.27 (s, 6 H), 3.09-3.21 (m, 1 H), 2.97 (t, *J* = 6.5 Hz, 2 H), 1.75-1.97 (m, 4 H), 1.39-1.64 (m, 2 H), 1.37 (d, *J* = 6.8 Hz, 6 H), 0.85-1.12 (m, 4 H).

Example 21



***N*²-[1-(4-Bromo-2-trifluoromethoxy-benzenesulfonyl)-pyrrolidin-3-yl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine**

Step A: Synthesis of 1-(4-bromo-2-trifluoromethoxy-benzenesulfonyl)-pyrrolidin-3-ylamine hydrochloride.

To a solution of pyrrolidin-3-yl-carbamic acid *tert*-butyl ester (1.00 g, 5.37 mmol) in CH₂Cl₂ (10 mL) was added diisopropylethylamine (1.96 mL, 5.92 mmol). The mixture was cooled at 0 °C and a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (2.01 g, 5.92 mmol) in CH₂Cl₂ (10 mL) was added below 10 °C. The reaction mixture was stirred at 4 °C for 15 min, dissolved in CHCl₃ and saturated aqueous NaHCO₃. The two phases were separated, the aqueous layer was extracted with CHCl₃ (twice). The combined organic layer was dried over MgSO₄, filtered, concentrated, and dried under reduced pressure to give a pale brown solid. To a solution of the above solid in CHCl₃ (50 mL) was added 4 M hydrogen chloride in EtOAc (50 mL). The mixture was stirred at ambient temperature for 1 hr, filtered, washed with EtOAc, and dried under reduced pressure to

give 1-(4-bromo-2-trifluoromethoxy-benzenesulfonyl)-pyrrolidin-3-ylamine hydrochloride (1.83 g, 80%) as a white solid.

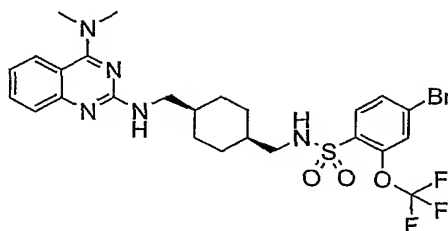
ESI MS m/e 388, M^+ ; 1H NMR (300 MHz, DMSO- d_6) δ 8.44 (brs, 3 H), 7.82-7.94 (m, 3 H), 3.76-3.84 (m, 1 H), 3.42-3.58 (m, 2 H), 3.23-3.40 (m, 2 H), 2.10-2.23 (m, 1 H), 1.88-2.02 (m, 1 H).

Step B: Synthesis of N^2 -[1-(4-bromo-2-trifluoromethoxy-benzenesulfonyl)-pyrrolidin-3-yl]- N^4,N^4 -dimethyl-quinazoline-2,4-diamine

Using the procedure for the step C of example 3, the title compound was obtained.

ESI MS m/e 560, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.82-7.89 (m, 2 H), 7.40-7.75 (m, 4 H), 7.08 (ddd, $J = 8.3, 6.8, 1.5$ Hz, 1 H), 4.83 (brs, 1 H), 4.53-4.64 (m, 1 H), 3.75 (dd, $J = 10.3, 5.8$ Hz, 1 H), 3.48-3.64 (m, 2 H), 3.44 (dd, $J = 10.3, 4.4$ Hz, 1 H), 3.27 (s, 6 H), 2.21-2.36 (m, 1 H), 1.86-2.00 (m, 1 H).

Example 22



***cis*-4-Bromo- N -{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide**

Step A: Synthesis of *cis*-[4-(*tert*-butoxycarbonylamino-methyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester.

To MeOH (220 mL) cooled at 0 °C was added thionyl chloride (52 mL) below 10 °C over 2.5 hr and the solution was stirred at 0 °C for 1 hr. To the reaction mixture was added *cis*-cyclohexane-1,4-dicarboxylic acid (30.0 g, 174 mmol) and the mixture was stirred at ambient temperature for 14 hr and concentrated. The residue was dissolved in $CHCl_3$, poured into saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated. A suspension of lithium aluminum hydride (13.2 g, 348 mmol) in THF (400 mL) was cooled at -20 °C. A solution of the above residue in THF (200 mL) was added

dropwise, and the mixture was stirred at ambient temperature for 3 hr. The reaction was quenched with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$, filtered through a pad of celite, and concentrated. To a solution of the above residue in toluene (500 mL) was added triphenylphosphine (37.2 g, 142 mmol). To the mixture cooled at 4 °C were added phthalimide (20.9 g, 142 mmol) and 40% diethyl azodicarboxylate (DEAD) in toluene (61.7 mL, 136 mmol) over 25 min. The reaction mixture was stirred at ambient temperature for 12 hr, poured into H_2O . The aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated. The precipitate was suspended in Et_2O , filtered, washed with MeOH and Et_2O , and dried under reduced pressure to give a white solid (16.5 g). To a suspension of the above solid (16.5 g, 41.0 mmol) in EtOH (735 mL) was added hydrazine hydrate (20.5 g, 410 mmol). The mixture was stirred at reflux for 2.5 hr, cooled, and concentrated. The precipitate was dissolved in 10% aqueous sodium hydroxide (120 mL) and 1, 4-dioxane (160 mL). To the mixture cooled on an ice-bath was added $(\text{Boc})_2\text{O}$ (30.4 g, 139 mmol) and the mixture was stirred at ambient temperature for 2.5 hr, and poured into H_2O . The aqueous layer was extracted with CHCl_3 (ten times). The combined organic layer was dried over MgSO_4 , filtered and concentrated. The precipitate was suspended in hexane, filtered, washed with hexane, and dried under reduced pressure to give *cis*-[4-(*tert*-butoxycarbonylamino-methyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester (5.10 g, 9%) as a white solid.

ESI MS m/e 365, $\text{M} + \text{Na}^+$; ^1H NMR (300 MHz, CDCl_3) δ 4.49-4.59 (m, 2 H), 3.05 (t, J = 6.6 Hz, 4 H), 1.29-1.69 (m, 28 H).

Step C: Synthesis of *cis*-(4-aminomethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester.

To a solution of *cis*-[4-(*tert*-butoxycarbonylamino-methyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester (2.55 g, 7.45 mmol) in CH_2Cl_2 (40 mL) was added 4 M hydrogen chloride in EtOAc (4 mL). The reaction mixture was stirred at ambient temperature for 5 hr and concentrated. The residue was dissolved in 1,4-dioxane (20 mL) and 10% aqueous sodium hydroxide (40 mL) and the resulting solution was cooled on an ice-bath. $(\text{Boc})_2\text{O}$ (829 mg, 3.80 mmol) was added dropwise and the mixture was stirred at ambient temperature for 3 h. The aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered and concentrated, and purified by flash chromatography (silica gel, 9% MeOH in CHCl_3) to give *cis*-(4-aminomethyl-

cyclohexylmethyl)-carbamic acid *tert*-butyl ester (255 mg, 14%) as a pale yellow oil.

ESI MS m/e 243, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 4.58 (brs, 1 H), 3.06 (t, $J = 6.7$ Hz, 2 H), 2.60 (d, $J = 5.9$ Hz, 2 H), 1.28-1.70 (m, 19 H).

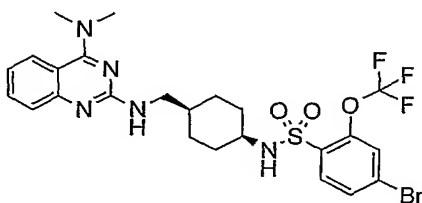
Step D: Synthesis of *cis*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester.

Using the procedure for the step G of example 1, the title compound was obtained. ESI MS m/e 414, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, $J = 7.8$ Hz, 1 H), 7.42-7.52 (m, 2 H), 7.02 (ddd, $J = 8.3, 6.3, 1.9$ Hz, 1 H), 4.52 (brs, 1 H), 3.45 (t, $J = 6.6$ Hz, 2 H), 3.27 (s, 6 H), 3.08 (t, $J = 6.5$ Hz, 2 H), 1.34-1.86 (m, 19 H).

Step E: Synthesis of *cis*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethoxy-benzenesulfonamide.

Using the procedure for the step H of example 1, the title compound was obtained. ESI MS m/e 616, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, $J = 8.9$ Hz, 1 H), 7.81 (d, $J = 7.8$ Hz, 1 H), 7.41-7.58 (m, 4 H), 7.03 (ddd, $J = 8.2, 6.6, 1.5$ Hz, 1 H), 3.41 (t, $J = 6.5$ Hz, 2 H), 3.50 (s, 6 H), 2.90 (d, $J = 7.3$ Hz, 2 H), 1.32-1.86 (m, 10 H).

Example 23



***cis*-4-Bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexyl}-2-trifluoromethoxy-benzenesulfonamide**

Step A: Synthesis of *cis*-(4-hydroxymethyl-cyclohexyl)-carbamic acid *tert*-butyl ester..

A suspension of *cis*-4-amino-cyclohexanecarboxylic acid (244 g, 1.70 mol) in MeOH (2.45 L) was cooled to $-8^\circ C$. Thionyl chloride (45.0 mL, 617 mmol) was added dropwise. The resulting solution was stirred at ambient temperature for 4.5 hr and concentrated to give a white solid. To a suspension of the above solid in $CHCl_3$ (3.00 L)

were added triethylamine (261 mL, 1.87 mol) and (Boc)₂O (409 g, 1.87 mol) successively. The reaction mixture was stirred at ambient temperature for 5 hr and poured into water. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (silica gel, CHCl₃ only to 10% MeOH in CHCl₃) to give a colorless oil (531 g). To a suspension cooled at -4 °C of lithium aluminum hydride (78.3 g, 2.06 mol) in Et₂O (7.9 L) was added a solution of above oil (530.9 g) in Et₂O (5.3 L) below 0 °C. The resulting suspension was stirred at ambient temperature for 2 hr. The reaction mixture was cooled on an ice-bath, quenched with cold water, filtered through a pad of celite. The filtrate was dried over MgSO₄, filtered, and concentrated. The precipitate was suspended in hexane (300 mL), filtered, washed with hexane, and dried under reduced pressure to give *cis*-(4-hydroxymethyl-cyclohexyl)-carbamic acid *tert*-butyl ester (301 g, 77%) as a white solid. ESI MS *m/e* 252, M + Na⁺; ¹H NMR (300 MHz, CDCl₃) δ 4.30-4.82 (m, 1 H), 3.75 (brs, 1 H), 3.51 (d, *J* = 6.2 Hz, 1 H), 1.52-1.77 (m, 7 H), 1.45 (s, 9 H), 1.16-1.36 (m, 2 H).

Step B: Synthesis of *cis*-[4-(benzyloxycarbonylamino-methyl)-cyclohexyl]-carbamic acid *tert*-butyl ester.

To a solution of *cis*-(4-hydroxymethyl-cyclohexyl)-carbamic acid *tert*-butyl ester (17.7 g, 77.2 mmol) in THF (245 mL) were added triphenylphosphine (20.2 g, 77.0 mmol) and phthalimide (11.4 g, 77.5 mmol) successively. The resulting suspension was cooled on an ice-bath and 40% diethyl azodicarboxylate (DEAD) in toluene was added over 1 hr. The reaction mixture was stirred at ambient temperature for 2.5 days, concentrated, and purified by flash chromatography (silica gel, 33% EtOAc in hexane) to give a white solid. To a suspension of above solid (27.5 g) in EtOH (275 mL) was added hydrazine hydrate (5.76 g, 115 mmol). The mixture was stirred at reflux for 2.25 hr, cooled, concentrated. The precipitate was dissolved in 10% aqueous sodium hydroxide (350 mL). The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered and concentrated. To a solution of the above residue in CHCl₃ (275 mL) was added triethylamine (8.54 g, 84.4 mmol). The resulting solution was cooled to 0 °C and ZCl (14.4 g, 84.4 mmol) was added below 5 °C. The reaction mixture was stirred at ambient temperature for 16 hr, and poured into saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (silica gel, 2%

MeOH in CHCl_3) to give *cis*-[4-(benzyloxycarbonylamino-methyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (25.3 g, 91%) as a colorless oil.

ESI MS m/e 385, $M + \text{Na}^+$; ^1H NMR (300 MHz, CDCl_3) δ 7.27-7.38 (m, 5 H), 5.09 (s, 2 H), 4.76-4.92 (m, 1 H), 4.42-4.76 (m, 1 H), 3.72 (brs, 1 H), 3.10 (t, $J = 6.4$ Hz, 2 H), 1.48-1.75 (m, 7 H), 1.44 (s, 9 H), 1.13-1.31 (m, 2 H).

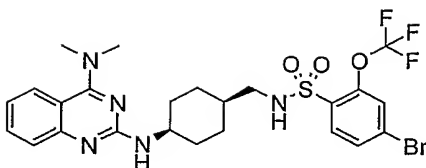
Step C: Synthesis of *cis*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexyl}-carbamic acid *tert*-butyl ester.

A mixture of *cis*-[4-(benzyloxycarbonylamino-methyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (4.00 g, 11.0 mmol) and 5% Pd/C (400 mg) in MeOH (40 mL) was stirred under hydrogen atmosphere at ambient temperature for 8.5 hr and at 50 °C for 12 hr, filtered through a pad of celite, and concentrated. The precipitate was suspended in hexane and the suspension was stirred at ambient temperature for 30 min. The solid was collected by filtration, washed with hexane, and dried (3.03 g). A mixture of (2-chloro-quinazolin-4-yl)-dimethyl-amine obtained in step B of example 1 (1.00 g, 4.82 mmol) and the above solid (1.65 g, 7.23 mmol) in 2-propanol (10 mL) was stirred at reflux for 5 days, poured into saturated aqueous NaHCO_3 , and the aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by flash chromatography (NH-silica gel, 20% EtOAc in hexane) to give *cis*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexyl}-carbamic acid *tert*-butyl ester (629 mg, 43%) as a pale yellow solid.

ESI MS m/e 400, $M + \text{H}^+$; ^1H NMR (300 MHz, CDCl_3) δ 7.81 (d, $J = 8.2$ Hz, 1 H), 7.42-7.56 (m, 2 H), 6.98-7.06 (m, 1 H), 4.64-4.75 (m, 1 H), 3.67-3.82 (m, 1 H), 3.29-3.44 (m, 2 H), 3.28 (s, 6 H), 1.50-1.78 (m, 7 H), 1.45 (s, 9 H), 1.21-1.42 (m, 2 H).

Step D: Synthesis of *cis*-4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexyl}-2-trifluoromethoxy-benzenesulfonamid.

Using the procedure for the step H of example 1, the title compound was obtained. ESI MS m/e 602, $M + \text{H}^+$; ^1H NMR (300 MHz, CDCl_3) δ 7.91 (d, $J = 8.9$ Hz, 1 H), 7.82 (dd, $J = 8.0, 1.0$ Hz, 1 H), 7.42-7.56 (m, 4 H), 7.04 (ddd, $J = 8.3, 6.6, 1.6$ Hz, 1 H), 3.44-3.50 (m, 1 H), 3.40 (t, $J = 6.0$ Hz, 2 H), 3.28 (s, 6 H), 1.22-1.78 (m, 9 H).

Example 24***cis*-4-Bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzenesulfonamide****Step A: Synthesis of *cis*-(4-amino-cyclohexylmethyl)-carbamic acid benzyl ester.**

To a solution of *cis*-[4-(benzyloxycarbonylamino-methyl)-cyclohexyl]-carbamic acid *tert*-butyl ester obtained in step C of example 23 (12.9 g, 35.6 mmol) in EtOAc (129 mL) was added 4 M hydrogen chloride in EtOAc (129 mL). The reaction mixture was stirred at ambient temperature for 3 hr, filtered, washed with EtOAc, and dried under reduced pressure. The solid was dissolved in saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (five times), dried over MgSO₄, filtered and concentrated, and dried under reduced pressure to give *cis*-(4-amino-cyclohexylmethyl)-carbamic acid benzyl ester (8.88 g, 95%) as a colorless oil.

ESI MS *m/e* 263, *M* + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.36 (s, 5 H), 5.12 (brs, 3 H), 2.96-3.32 (m, 3 H), 1.36-1.98 (m, 9 H).

Step B: Synthesis of *cis*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester.

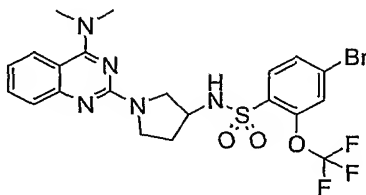
Using the procedure for the step G of example 1, the title compound was obtained. ESI MS *m/e* 434, *M* + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (d, *J* = 9.0 Hz, 1 H), 7.26-7.52 (m, 7 H), 7.01 (ddd, *J* = 8.2, 6.5, 1.7 Hz, 1 H), 5.10 (s, 2 H), 4.93-5.06 (m, 1 H), 4.82-4.93 (m, 1 H), 4.18-4.28 (m, 1 H), 3.26 (s, 6 H), 3.11 (t, *J* = 6.3 Hz, 2 H), 1.80-1.93 (m, 2 H), 1.52-1.73 (m, 5 H), 1.23-1.40 (m, 2 H).

Step C: Synthesis of *cis*-4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzenesulfonamide.

Using the procedure for the step D of example 3, the title compound was obtained.

ESI MS m/e 602, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, $J = 8.9$ Hz, 1 H), 7.81 (dd, $J = 8.3, 1.3$ Hz, 1 H), 7.38-7.59 (m, 4 H), 7.02 (ddd, $J = 8.2, 6.8, 1.2$ Hz, 1 H), 4.75-5.24 (m, 1 H), 4.16-4.27 (m, 1 H), 3.27 (s, 6 H), 2.86 (d, $J = 6.4$ Hz, 2 H), 1.78-1.91 (m, 2 H), 1.51-1.70 (m, 5 H), 1.21-1.38 (m, 2 H).

Example 25



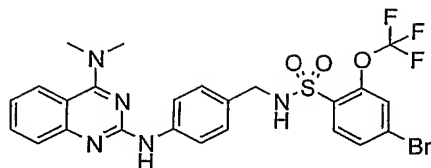
4-Bromo-*N*-[1-(4-dimethylamino-quinazolin-2-yl)-pyrrolidin-3-yl]-2-trifluoromethoxy-benzenesulfonamide

Step A: Synthesis of [1-(4-dimethylamino-quinazolin-2-yl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester.

Using the procedure for the step G of example 1, the title compound was obtained. ESI MS m/e 358, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, $J = 8.2$ Hz, 1 H), 7.45-7.54 (m, 2 H), 6.98-7.05 (m, 1 H), 4.67-4.80 (m, 1 H), 4.25-4.40 (m, 1 H), 3.85-3.94 (m, 1 H), 3.68-3.79 (m, 2 H), 3.52-3.62 (m, 1 H), 3.27 (s, 6 H), 2.16-2.28 (m, 1 H), 1.86-2.01 (m, 1 H), 1.45 (s, 9 H).

Step B: Synthesis of 4-bromo-*N*-[1-(4-dimethylamino-quinazolin-2-yl)-pyrrolidin-3-yl]-2-trifluoromethoxy-benzenesulfonamide.

Using the procedure for the step H of example 1, the title compound was obtained. ESI MS m/e 560, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, $J = 8.4$ Hz, 1 H), 7.81 (d, $J = 8.1$ Hz, 1 H), 7.44-7.58 (m, 4 H), 7.03 (ddd, $J = 8.4, 5.7, 2.6$ Hz, 1 H), 4.76-5.04 (m, 1 H), 3.96-4.11 (m, 1 H), 3.70-3.82 (m, 2 H), 3.58-3.68 (m, 1 H), 3.45-3.54 (m, 1 H), 3.25 (s, 6 H), 2.11-2.24 (m, 1 H), 1.86-1.99 (m, 1 H).

Example 26

4-Bromo-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-benzyl]-2-trifluoromethoxy-benzene sulfonamide

Step A: Synthesis of (4-amino-benzyl)-carbamic acid *tert*-butyl ester.

To a solution of 4-aminomethyl-phenylamine (1.00 g, 8.19 mmol) in CHCl_3 (10 mL) was added triethylamine (870 mg, 8.60 mmol). After cooling on an ice-bath, $(\text{Boc})_2\text{O}$ (1.88 g, 8.61 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 55 min and poured into saturated aqueous NaHCO_3 . The aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by flash chromatography (silica gel, 9% MeOH in CHCl_3) to give (4-amino-benzyl)-carbamic acid *tert*-butyl ester (1.79 g, 99%) as a yellow solid.

ESI MS m/e 245, $\text{M} + \text{Na}^+$; ^1H NMR (200 MHz, CDCl_3) δ 7.07 (d, $J = 8.4$ Hz, 2 H), 6.63 (d, $J = 8.4$ Hz, 2 H), 4.76 (brs, 1 H), 4.18 (d, $J = 5.3$ Hz, 2 H), 3.65 (brs, 2 H), 1.45 (s, 9 H).

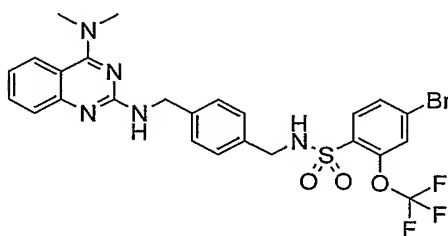
Step B: Synthesis of 4-bromo-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-benzyl]-2-trifluoromethoxy-benzenesulfonamide.

A mixture of (2-chloro-quinazolin-4-yl)-dimethyl-amine obtained in step B of example 1 (1.00 g, 4.82 mmol) and (4-amino-benzyl)-carbamic acid *tert*-butyl ester (1.28 g, 5.76 mmol) in 2-propanol (10 mL) was stirred at reflux for 3 hr, cooled, poured into saturated aqueous NaHCO_3 , and the aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by flash chromatography (NH-silica gel, 20% EtOAc in hexane) to give a pale yellow solid (2.32 g). To a solution of the above solid (750 mg, 1.91 mmol) in EtOAc (7 mL) was added 4 M hydrogen chloride in EtOAc (7 mL). The mixture was stirred at ambient

temperature for 2 hr, concentrated to give a white solid. To a suspension of the above solid in CH_2Cl_2 (5 mL) was added diisopropylethylamine (730 μL , 4.19 mmol). The mixture was cooled on an ice-bath and a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (777 mg, 2.29 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred on an ice-bath for 9 hr, poured into saturated aqueous NaHCO_3 . The aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by medium-pressure liquid chromatography (NH-silica gel, 20% EtOAc in hexane) to give 4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-benzyl]-2-trifluoromethoxy-benzenesulfonamide (519 mg, 56%) as a pale yellow solid.

ESI MS m/e 618, $M + \text{Na}^+$; ^1H NMR (300 MHz, CDCl_3) δ 7.88 (t, $J = 9.0$ Hz, 2 H), 7.64 (d, $J = 8.6$ Hz, 2 H), 7.48-7.61 (m, 4 H), 6.98-7.20 (m, 4 H), 4.96 (brs, 1 H), 4.13 (s, 2 H), 3.34 (s, 6 H).

Example 27



4-Bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-benzyl}-2-trifluoromethoxy-benzenesulfonamide

Step A: Synthesis of (4-aminomethyl-benzyl)-carbamic acid *tert*-butyl ester.

To a solution of 4-aminomethyl-benzylamine (15.0 g, 110 mmol) in CHCl_3 (85 mL) was added a solution of $(\text{Boc})_2\text{O}$ (3.03 g, 13.9 mmol) in CHCl_3 (45 mL) dropwise over 3.5 hr. The reaction mixture was stirred at ambient temperature for 13 hr, and concentrated. After dissolution with H_2O , the aqueous layer was extracted with EtOAc (three times). The combined organic layer was washed with H_2O (three times), dried over MgSO_4 , filtered, and concentrated to give (4-aminomethyl-benzyl)-carbamic acid *tert*-butyl ester (3.20 g, 12%) as a white solid.

ESI MS m/e 237, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.30 (m, 4 H), 4.86-5.02 (m, 1 H), 4.29 (d, $J = 5.8$ Hz, 2 H), 3.84 (s, 2 H), 1.46 (s, 9 H).

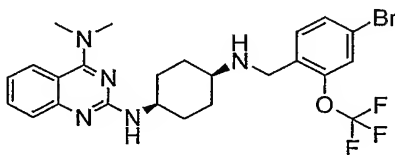
Step B: Synthesis of {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester.

Using the procedure for the step G of example 1, the title compound was obtained. ESI MS m/e 408, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, $J = 8.2$ Hz, 1 H), 7.47-7.55 (m, 2 H), 7.37 (d, $J = 8.0$ Hz, 2 H), 7.24 (d, $J = 8.0$ Hz, 2 H), 7.05-7.10 (m, 1 H), 5.35-5.45 (m, 1 H), 4.90-5.04 (m, 1 H), 4.72 (d, $J = 5.8$ Hz, 2 H), 4.31 (d, $J = 5.8$ Hz, 2 H), 3.27 (s, 6 H), 1.49 (s, 9 H).

Step C: Synthesis of 4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-benzyl}-2-trifluoromethoxy-benzenesulfonamide.

Using the procedure for the step H of example 1, the title compound was obtained. ESI MS m/e 610, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, $J = 8.4$ Hz, 2 H), 7.44-7.54 (m, 4 H), 7.29 (d, $J = 7.9$ Hz, 2 H), 7.11 (d, $J = 8.1$ Hz, 2 H), 7.06 (ddd, $J = 8.3, 6.3, 2.0$ Hz, 1 H), 4.67 (d, $J = 5.9$ Hz, 2 H), 4.15 (s, 2 H), 3.26 (s, 6 H).

Example 28



cis- N^2 -[4-(4-bromo-2-trifluoromethoxy-benzylamino)-cyclohexyl]- N^4,N^4 -dimethyl-quinazoline-2,4-diamine

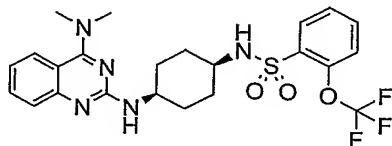
Step A: Synthesis of *cis*- N^2 -[4-(4-bromo-2-trifluoromethoxy-benzylamino)-cyclohexyl]- N^4,N^4 -dimethyl-quinazoline-2,4-diamine.

Using the procedure for the step B of example 15, the title compound was obtained.

ESI MS m/e 560, $M + Na^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, $J = 7.9, 0.9$ Hz, 1 H),

7.36-7.51 (m, 5 H), 7.01 (ddd, $J = 8.3, 6.4, 1.9$ Hz, 1 H), 4.95-5.18 (m, 1 H), 4.08-4.22 (m, 1 H), 3.81 (s, 2 H), 3.25 (s, 6 H), 2.55-2.70 (m, 1 H), 1.65-1.90 (m, 6 H), 1.29-1.65 (m, 2 H).

Example 29

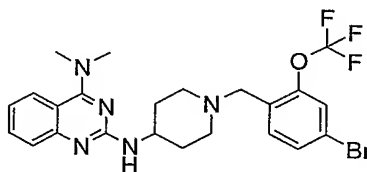


***cis-N*-[4-(4-Dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzenesulfonamide**

Step A: Synthesis of *cis-N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzenesulfonamide.

Using the procedure for the step A of example 20, the title compound was obtained. ESI MS m/e 532, $M + Na^+$; 1H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, $J = 8.1, 1.9$ Hz, 1 H), 7.81 (dd, $J = 8.4, 1.4$ Hz, 1 H), 7.36-7.66 (m, 5 H), 7.03 (ddd, $J = 8.3, 6.7, 1.5$ Hz, 1 H), 4.72-5.07 (m, 2 H), 3.95-4.10 (m, 1 H), 3.32-3.48 (m, 1 H), 3.25 (s, 6 H), 1.37-2.17 (m, 8 H).

Example 30



***N*²-[1-(4-Bromo-2-trifluoromethoxy-benzyl)-piperidin-4-yl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine**

Step A: Synthesis of *N*²-(1-benzyl-piperidin-4-yl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine.

Using the procedure for the step G of example 1, the title compound was obtained. ESI MS m/e 362, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, $J = 7.6$ Hz, 1 H), 7.20-7.52 (m, 7 H), 6.97-7.05 (m, 1 H), 4.74-4.90 (m, 1 H), 3.90-4.05 (m, 1 H), 3.53 (s, 2 H), 3.26 (s, 6 H), 2.78-2.90 (m, 2 H), 2.02-2.24 (m, 4 H), 1.48-1.62 (m, 2 H).

Step B: Synthesis of N^4, N^4 -dimethyl- N^2 -piperidin-4-yl-quinazoline-2,4-diamine.

To a solution of N^2 -(1-benzyl-piperidin-4-yl)- N^4, N^4 -dimethyl-quinazoline-2,4-diamine (1.80 g, 4.98 mmol) in MeOH (18 mL) was added 20% $Pd(OH)_2$ (360 mg). The mixture was stirred at 50 °C under hydrogen atmosphere for 3 days, filtered through a pad of celite, and concentrated to give N^4, N^4 -dimethyl- N^2 -piperidin-4-yl-quinazoline-2,4-diamine (1.33 g, 99%) as a pale yellow solid.

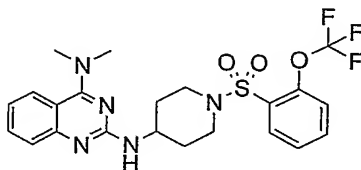
ESI MS m/e 272, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, $J = 8.6$ Hz, 1 H), 7.43-7.62 (m, 2 H), 7.15 (t, $J = 8.2$ Hz, 1 H), 4.12-4.29 (m, 1 H), 3.29-3.47 (m, 2 H), 3.37 (s, 6 H), 2.96-3.12 (m, 2 H), 2.20-2.34 (m, 2 H), 1.79-1.97 (m, 2 H).

Step C: Synthesis of N^2 -[1-(4-bromo-2-trifluoromethoxy-benzyl)-piperidin-4-yl]- N^4, N^4 -dimethyl-quinazoline-2,4-diamine.

Using the procedure for the step B of example 15, the title compound was obtained.

ESI MS m/e 546, $M + Na^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, $J = 8.7, 0.9$ Hz, 1 H), 7.34-7.54 (m, 5 H), 7.01 (ddd, $J = 8.3, 6.6, 1.6$ Hz, 1 H), 4.76-4.95 (m, 1 H), 3.87-4.06 (m, 1 H), 3.52 (s, 2 H), 3.25 (s, 6 H), 2.71-2.86 (m, 2 H), 2.17-2.33 (m, 2 H), 1.97-2.12 (m, 2 H), 1.44-1.61 (m, 2 H).

Example 31

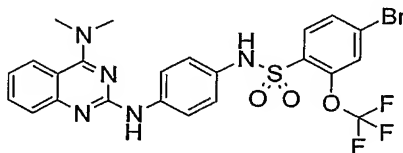


N^4, N^4 -Dimethyl- N^2 -[1-(2-trifluoromethoxy-benzenesulfonyl)-piperidin-4-yl]-quinazoline-2,4-diamine

Step A: Synthesis of *N*^d,*N*^d-dimethyl-*N*²-[1-(2-trifluoromethoxy-benzenesulfonyl)-piperidin-4-yl]-quinazoline-2,4-diamine.

Using the procedure for the step A of example 20, the title compound was obtained. ESI MS *m/e* 518, *M* + *Na*⁺; ¹H NMR (300 MHz, CDCl₃) δ 8.02 (dd, *J* = 7.9, 1.9 Hz, 1 H), 7.81 (dd, *J* = 8.4, 0.7 Hz, 1 H), 7.34-7.67 (m, 5 H), 7.04 (ddd, *J* = 8.3, 6.7, 1.5 Hz, 1 H), 4.81 (brs, 1 H), 3.95-4.12 (m, 1 H), 3.78 (d, *J* = 12.8 Hz, 2 H), 3.25 (s, 6 H), 2.85-3.05 (m, 2 H), 2.05-2.28 (m, 2 H), 1.50-1.71 (m, 2 H).

Example 32



4-Bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-phenyl]-2-trifluoromethoxy-benzenesulfonamide

Step A: Synthesis of [4-(4-dimethylamino-quinazolin-2-ylamino)-phenyl]-carbamic acid *tert*-butyl ester.

Using the procedure for the step G of example 1, the title compound was obtained. ESI MS *m/e* 402, *M* + *Na*⁺; ¹H NMR (300 MHz, CDCl₃) δ 10.05 (brs, 1 H), 7.94 (d, *J* = 8.4 Hz, 1 H), 7.50-7.66 (m, 4 H), 7.23-7.38 (m, 3 H), 6.57-6.64 (m, 1 H), 3.48 (s, 6 H), 1.53 (s, 9 H).

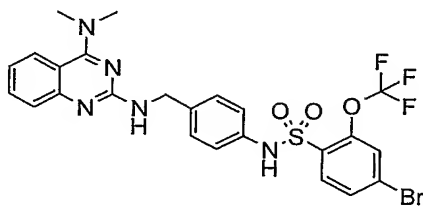
Step B: Synthesis of 4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-phenyl]-2-trifluoromethoxy-benzenesulfonamide

To a suspension of [4-(4-dimethylamino-quinazolin-2-ylamino)-phenyl]-carbamic acid *tert*-butyl ester (380 mg, 1.00 mmol) in EtOAc (4 mL) and CH₂Cl₂ (4 mL) was added 4 M hydrogen chloride in EtOAc (4 mL). The mixture was stirred at ambient temperature for 4 hr and concentrated to give a white solid. The solid was alkalized with saturated aqueous NaHCO₃, filtered, washed with H₂O and hexane, and dried at 50 °C under reduced

pressure. To a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (680 mg, 2.00 mmol) in CH_2Cl_2 (30 mL) was added PVP (8 mL). To the resulting suspension was added a solution of the above solid in CH_2Cl_2 (5 mL). The mixture was stirred at ambient temperature for 10.5 hr and filtered. The filtrate was washed with saturated aqueous NaHCO_3 , dried over MgSO_4 , filtered, concentrated, and purified by medium-pressure liquid chromatography (NH-silica gel, EtOAc) to give a solid. The solid was washed with Et_2O and dried at 50 °C under reduced pressure to give 4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-phenyl]-2-trifluoromethoxy-benzenesulfonamide (202 mg, 35%) as a pale yellow solid.

ESI MS m/e 582, $M + H^+$; ^1H NMR (300 MHz, CDCl_3) δ 7.88 (d, $J = 8.4$ Hz, 1 H), 7.73 (d, $J = 8.4$ Hz, 1 H), 7.64 (d, $J = 8.9$ Hz, 2 H), 7.51-7.58 (m, 3 H), 7.44 (dd, $J = 8.4$, 1.7 Hz, 1 H), 7.07-7.24 (m, 1 H), 7.02 (d, $J = 8.9$ Hz, 2 H), 3.32 (s, 6 H).

Example 33



4-Bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-phenyl}-2-trifluoromethoxy-benzenesulfonamide

Step A: Synthesis of [4-(*tert*-butoxycarbonylamino-methyl)-phenyl]-carbamic acid benzyl ester.

To a solution of 4-aminomethyl-phenylamine (3.00 g, 24.6 mmol) in CHCl_3 (30 mL) was added triethylamine (2.61 g, 25.8 mmol). After cooling on an ice-bath, $(\text{Boc})_2\text{O}$ (5.63 g, 25.8 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 55 min and poured into saturated aqueous NaHCO_3 . The aqueous layer was extracted with CHCl_3 (three times) and the combined organic layer was dried over MgSO_4 , filtered, and concentrated to give a pale yellow oil. To a solution of the above oil in CHCl_3 (30 mL) was added diisopropylethylamine (3.33 g, 25.8 mmol). The resulting solution was cooled to 4 °C and ZCl (4.40 g, 25.8 mmol) was added below 10 °C over 5 min. The reaction mixture was stirred at ambient temperature for 12 hr, and poured into

saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (silica gel, 2% MeOH in CHCl₃) to give [4-(*tert*-butoxycarbonylamino-methyl)-phenyl]-carbamic acid benzyl ester (2.64 g, 30%) as a white solid.

ESI MS *m/e* 379, M + Na⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.11-7.44 (m, 9 H), 6.76 (brs, 1 H), 5.19 (s, 2 H), 4.81 (brs, 1 H), 4.25 (d, *J* = 5.1 Hz, 2 H), 1.45 (s, 9 H).

Step B: Synthesis of (4-aminomethyl-phenyl)-carbamic acid benzyl ester hydrochloride.

A solution of [4-(*tert*-butoxycarbonylamino-methyl)-phenyl]-carbamic acid benzyl ester (1.25 g, 3.51 mmol) in EtOAc (20 mL) was cooled on an ice-bath and 4 M hydrogen chloride in EtOAc (20 mL) was added. The mixture was stirred at ambient temperature for 20 min. The precipitate was collected by filtration, washed with EtOAc, and dried under reduced pressure to give (4-aminomethyl-phenyl)-carbamic acid benzyl ester hydrochloride (957 mg, 93%) as a white solid.

ESI MS *m/e* 279, M + Na⁺; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.90 (s, 1 H), 8.37 (brs, 3 H), 7.29-7.55 (m, 9 H), 5.15 (s, 2 H), 3.85-4.01 (m, 2 H).

Step C: Synthesis of {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-phenyl}-carbamic acid benzyl ester.

Using the procedure for the step C of example 3, the title compound was obtained. ESI MS *m/e* 428, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.82 (d, *J* = 7.5 Hz, 1 H), 7.25-7.52 (m, 11 H), 6.98-7.07 (m, 1 H), 6.74 (brs, 1 H), 5.28 (brs, 1 H), 5.19 (s, 2 H), 4.65 (d, *J* = 5.9 Hz, 2 H), 3.25 (s, 6 H).

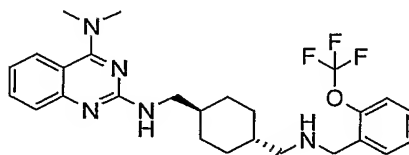
Step D: Synthesis of 4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-phenyl}-2-trifluoromethoxy-benzenesulfonamide.

To a solution of {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-phenyl}-carbamic acid benzyl ester (318 mg, 0.744 mmol) in MeOH (3 mL) was added 5% Pd/C (30 mg). The mixture was stirred at 50 °C under hydrogen atmosphere for 41.5 hr, filtered through a pad of celite, and concentrated. To a solution of 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (505 mg, 1.49 mmol) in CH₂Cl₂ (12 mL) was added PVP (6 mL).

To the resulting suspension was added a solution of the above residue in CH_2Cl_2 (10 mL). The mixture was stirred at ambient temperature for 1.5 days, filtered, poured into saturated aqueous NaHCO_3 . The aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by medium-pressure liquid chromatography (NH-silica gel, 33% EtOAc in hexane) to give 4-bromo-*N*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-phenyl}-2-trifluoromethoxy-benzenesulfonamide (330 mg, 74%) as a pale brown solid.

ESI MS m/e 596, $M + H^+$; ^1H NMR (300 MHz, CDCl_3) δ 7.83 (d, $J = 8.4$ Hz, 1 H), 7.77 (d, $J = 8.4$ Hz, 1 H), 7.41-7.60 (m, 4 H), 7.22 (d, $J = 8.6$ Hz, 2 H), 7.08-7.18 (m, 1 H), 6.99 (d, $J = 8.6$ Hz, 2 H), 4.56 (d, $J = 5.6$ Hz, 2 H), 3.34 (s, 6 H).

Example 34

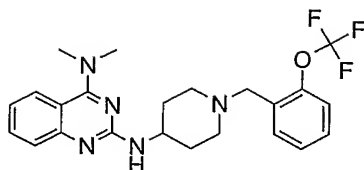


***trans*-*N*⁴,*N*⁴-Dimethyl-*N*²-{4-[(2-trifluoromethoxy-benzylamino)-methyl]-cyclohexylmethyl}-quinazoline-2,4-diamine**

Step A: Synthesis of *trans*-*N*⁴,*N*⁴-dimethyl-*N*²-{4-[(2-trifluoromethoxy-benzylamino)-methyl]-cyclohexylmethyl}-quinazoline-2,4-diamine.

Using the procedure for the step B of example 15, the title compound was obtained.

ESI MS m/e 510, $M + Na^+$; ^1H NMR (300 MHz, CDCl_3) δ 7.80 (d, $J = 8.2$ Hz, 1 H), 7.39-7.57 (m, 3 H), 7.15-7.35 (m, 3 H), 7.02 (ddd, $J = 8.3, 6.0, 2.2$ Hz, 1 H), 3.83 (s, 2 H), 3.35 (t, $J = 6.3$ Hz, 2 H), 3.27 (s, 6 H), 2.45 (d, $J = 6.5$ Hz, 2 H), 1.69-2.04 (m, 4 H), 1.37-1.69 (m, 2 H), 0.84-1.12 (m, 4 H).

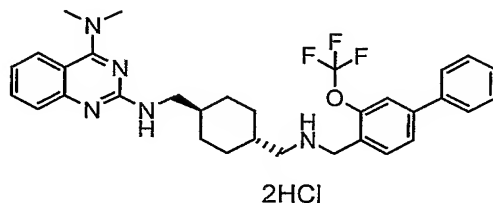
Example 35

***N^t,N^t*-Dimethyl-*N²*-[1-(2-trifluoromethoxy-benzyl)-piperidin-4-yl]-quinazoline-2,4-diamine**

Step A: Synthesis of *N^t,N^t*-dimethyl-*N²*-[1-(2-trifluoromethoxy-benzyl)-piperidin-4-yl]-quinazoline-2,4-diamine.

Using the procedure for the step B of example 15, the title compound was obtained.

ESI MS *m/e* 468, *M* + *Na*⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, *J* = 7.8 Hz, 1 H), 7.37-7.63 (m, 3 H), 7.17-7.35 (m, 3 H), 7.02 (ddd, *J* = 8.3, 6.4, 1.9 Hz, 1 H), 5.12 (brs, 1 H), 3.86-4.07 (m, 1 H), 3.60 (s, 2 H), 3.26 (s, 6 H), 2.74-2.94 (m, 2 H), 2.18-2.37 (m, 2 H), 1.98-2.15 (m, 2 H), 1.45-1.69 (m, 2 H).

Example 36

***trans*-*N^t,N^t*-Dimethyl-*N²*-(4-[(3-trifluoromethoxy-biphenyl-4-ylmethyl)-amino]-methyl)-cyclohexylmethyl-quinazoline-2,4-diamine dihydrochloride**

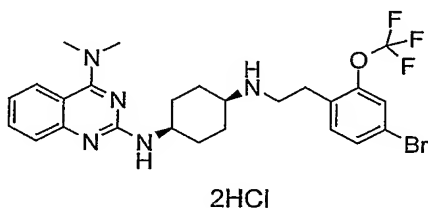
Step A: Synthesis of *trans*-*N^t,N^t*-dimethyl-*N²*-(4-[(3-trifluoromethoxy-biphenyl-4-ylmethyl)-amino]-methyl)-cyclohexylmethyl-quinazoline-2,4-diamine-dihydrochloride.

To a solution of *trans*-*N²*-{4-[(4-bromo-2-trifluoromethoxy-benzylamino)-methyl]-cyclohexylmethyl}-*N^t,N^t*-dimethyl-quinazoline-2,4-diamine obtained in step B of example

15 (300 mg, 0.529 mol) in toluene (6.6 mL) were added MeOH (2.2 mL), 2 M aqueous K_2CO_3 (2.2 mL), phenylboronic acid (77 mg, 0.635 mmol), and tetrakis (triphenylphosphine) palladium (61 mg, 0.053 mmol). The reaction mixture was stirred at 130 °C for 12 hr. The mixture was poured into water, and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated and, purified by flash chromatography (NH-silica gel, 33% $CHCl_3$ in hexane and silica gel, 9% MeOH in $CHCl_3$) to give pale yellow oil. To a solution of above oil in EtOAc (2 mL) was added 4 M hydrogen chloride in EtOAc (0.1 mL). The mixture was stirred at ambient temperature for 20 min and concentrated. A solution of the residue in Et_2O (2 mL) was stirred at ambient temperature for 30 min. The precipitate was collected by filtration, washed with Et_2O , and dried under reduced pressure to give *trans*- N^4,N^4 -dimethyl- N^2 -(4-[(3-trifluoromethoxy-biphenyl-4-ylmethyl)-amino]-methyl)-cyclohexylmethyl)-quinazoline-2,4-diamine dihydrochloride (70 mg, 21%) as a white solid.

ESI MS m/e 564, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 13.27 (s, 1 H), 9.96 (brs, 2 H), 8.17-8.32 (m, 2 H), 7.89 (d, $J = 7.9$ Hz, 1 H), 7.34-7.64 (m, 9 H), 7.20 (t, $J = 7.7$ Hz, 1 H), 4.29 (brs, 2 H), 3.50 (s, 6 H), 3.28 (t, $J = 6.1$ Hz, 2 H), 2.69 (brs, 2 H), 1.79-2.11 (m, 4 H), 1.44-1.68 (m, 2 H), 0.91-1.16 (m, 4 H).

Example 37



cis- N^2 -{4-[2-(4-Bromo-2-trifluoromethoxy-phenyl)-ethylamino]-cyclohexyl}- N^4,N^4 -dimethyl-quinazoline-2,4-diamine dihydrochloride

Step A: Synthesis of (4-bromo-2-trifluoromethoxy-phenyl)-acetaldehyde.

To a suspension of (methoxymethyl) triphenylphosphonium chloride (5.29 g, 14.9 mol) in Et_2O (50 mL) was added 1.8 M phenyl lithium in 30% Et_2O in cyclohexane (8.58 mL, 15.5 mmol). The mixture was stirred at ambient temperature for 10 min. To the

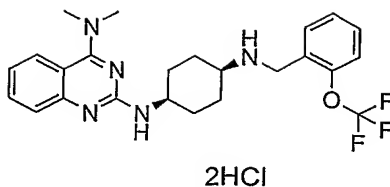
reaction mixture was added 4-bromo-2-trifluoromethoxy-benzaldehyde (4 g, 14.9 mmol) in Et₂O (18 mL). The mixture was stirred at ambient temperature for 4 hr, filtrated, and concentrated. To the above residue was added 10% H₂SO₄ in AcOH (40 mL). The mixture was stirred at ambient temperature for 90 min. The solution was poured into H₂O, and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was washed with saturated aqueous NaHCO₃, washed with brine, dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (silica gel, 9% EtOAc in hexane) to give (4-bromo-2-trifluoromethoxy-phenyl)-acetaldehyde (1.25 g, 30 %) as a pale brown oil.

ESI MS *m/e* 284, *M* + H⁺; ¹H NMR (200 MHz, CDCl₃) δ 9.74 (t, *J* = 1.5 Hz, 1 H), 7.41-7.51 (m, 2 H), 7.16 (d, *J* = 8.4 Hz, 1 H), 3.75 (d, *J* = 1.5 Hz, 2 H).

Step B: Synthesis of *cis*-*N*²-{4-[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethylamino]-cyclohexyl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

To a suspension of *cis*-*N*²-(4-amino-cyclohexyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine obtained in step C of example 9 (300 mg, 1.05 mmol) in CH₂Cl₂ (3 mL) were added (4-bromo-2-trifluoromethoxy-phenyl)-acetaldehyde (357 mg, 1.26 mmol), AcOH (76 mg, 1.26 mmol), and NaBH(OAc)₃ (334 mg, 1.57 mmol). The reaction mixture was stirred at ambient temperature for 4.5 hr. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 50% EtOAc in hexane) to give a pale yellow solid. To a solution of above solid in EtOAc (0.8 mL) was added 4 M hydrogen chloride in EtOAc (0.25 mL). The mixture was stirred at ambient temperature for 30 min and concentrated. A solution of the residue in Et₂O (2 mL) was stirred at ambient temperature for 30 min. The precipitate was collected by filtration, washed with Et₂O, and dried under reduced pressure to give *cis*-*N*²-{4-[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethylamino]-cyclohexyl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride (161 mg, 25%) as a white solid.

ESI MS *m/e* 552, *M* (free)⁺; ¹H NMR (200 MHz, CDCl₃) δ 12.66 (brs, 1 H), 9.91 (brs, 2 H), 8.71 (brs, 1 H), 7.93 (d, *J* = 6.6 Hz, 1 H), 7.19-7.77 (m, 6 H), 4.31 (brs, 1 H), 3.54 (s, 6 H), 3.09-3.78 (m, 5 H), 2.00-2.48 (m, 6 H), 1.62-1.96 (m, 2 H).

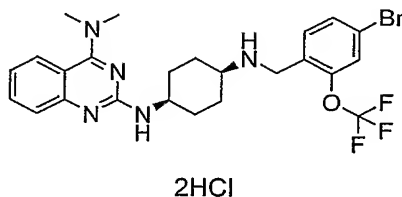
Example 38

***cis*-N^t,N^t-Dimethyl-N²-[4-(2-trifluoromethoxy-benzylamino)-cyclohexyl]-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-N^t,N^t-dimethyl-N²-[4-(2-trifluoromethoxy-benzylamino)-cyclohexyl]-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS *m/e* 460, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 8.68 (d, *J* = 7.6 Hz, 1 H), 8.19-8.33 (m, 1 H), 7.95 (d, *J* = 8.2 Hz, 1 H), 7.66 (t, *J* = 7.7 Hz, 1 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 7.18-7.44 (m, 4 H), 4.35 (s, 2 H), 4.15-4.47 (m, 1 H), 3.53 (s, 6 H), 3.02-3.31 (m, 1 H), 1.95-2.37 (m, 6 H), 1.51-1.85 (m, 2 H).

Example 39

***cis*-N²-[4-(4-Bromo-2-trifluoromethoxy-benzylamino)-cyclohexyl]-N^t,N^t-dimethyl-quinazoline-2,4-diamine dihydrochloride**

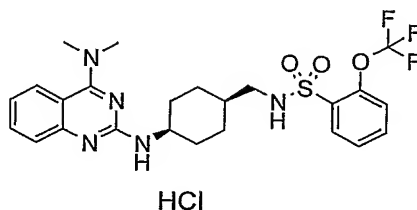
Step A: Synthesis of *cis*-N²-[4-(4-bromo-2-trifluoromethoxy-benzylamino)-cyclohexyl]-N^t,N^t-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of example 2, the title compound was obtained.

ESI MS *m/e* 538, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 8.77 (d, *J* = 7.5 Hz, 1 H), 8.11 (d, *J* = 8.4 Hz, 1 H), 7.92 (d, *J* = 8.6 Hz, 1 H), 7.67 (t, *J* = 7.7 Hz, 1 H), 7.41-7.53 (m,

2 H), 7.37 (s, 1 H), 7.28 (t, $J = 7.8$ Hz, 1 H), 4.19-4.40 (m, 1 H), 4.26 (s, 2 H), 3.52 (s, 7 H), 3.07-3.25 (m, 1 H), 2.00-2.39 (m, 6 H), 1.61-1.88 (m, 2 H).

Example 40



***cis*-N-[4-(4-Dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzenesulfonamide hydrochloride**

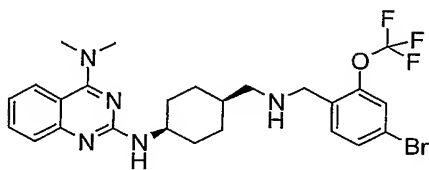
Step A: Synthesis of *cis*-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzenesulfonamide hydrochloride.

To a solution of *cis*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester obtained in step B of example 24 (4.57 g, 10.5 mmol) in MeOH (46 mL) was added 5% Pd/C (460 mg). The mixture was stirred at 50 °C under hydrogen atmosphere for 3 days, filtered, and concentrated to give a white solid (3.79 g). To a solution of the above solid (500 mg, 1.67 mmol) in CH₂Cl₂ (5 mL) was added diisopropylethylamine (440 μL, 2.53 mmol). The mixture was cooled on an ice-bath and a solution of 2-trifluoromethoxy-benzenesulfonyl chloride (457 mg, 1.75 mmol) in CH₂Cl₂ (2 mL) was added dropwise. The reaction mixture was stirred on an ice-bath for 10 hr. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, purified by medium-pressure liquid chromatography (NH-silica gel, 33% EtOAc in hexane), and concentrated. To a solution of the residue in EtOAc (1 mL) was added 4 M hydrogen chloride in EtOAc (5 mL). The reaction mixture was stirred at ambient temperature for 30 min, and concentrated. A solution of the residue in Et₂O (10 mL) was stirred at ambient temperature for 1 hr and the precipitate was collected by filtration to give *cis*-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzenesulfonamide hydrochloride (262 mg, 34%) as a white solid.

ESI MS m/e 524, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.18 (s, 1 H), 8.75 (d, $J =$

7.6 Hz, 1 H), 8.03 (dd, $J = 8.0, 1.7$ Hz, 1 H), 7.89 (d, $J = 8.2$ Hz, 1 H), 7.56-7.71 (m, 2 H), 7.34-7.55 (m, 3 H), 7.24 (t, $J = 7.5$ Hz, 1 H), 4.99 (t, $J = 6.5$ Hz, 1 H), 4.20-4.33 (m, 1 H), 3.50 (s, 6 H), 2.88 (t, $J = 6.3$ Hz, 2 H), 1.78-1.99 (m, 2 H), 1.38-1.77 (m, 7 H).

Example 41



2HCl

***cis*-N²-{4-[(4-Bromo-2-trifluoromethoxy-benzylamino)-methyl]-cyclohexyl}-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

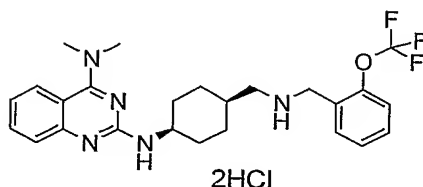
Step A: Synthesis of *cis*-N²-{4-[(4-bromo-2-trifluoromethoxy-benzylamino)-methyl]-cyclohexyl}-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

To a solution of *cis*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester obtained in step B of example 24 (4.57 g, 10.5 mmol) in MeOH (46 mL) was added 5% Pd/C (460 mg). The mixture was stirred at 50 °C under hydrogen atmosphere for 3 days, filtered, and concentrated to give a colorless solid (3.79 g). To a solution of the above solid (500 mg, 1.67 mmol) in CH₂Cl₂ (5 mL) were added 4-bromo-2-trifluoromethoxy-benzaldehyde obtained in step A of example 13 (449 mg, 1.67 mmol), AcOH (100 mg, 1.67 mmol), and NaBH(OAc)₃ (531 g, 2.51 mmol). The reaction mixture was stirred at ambient temperature with CaCl₂ tube for 9 hr, poured into saturated aqueous NaHCO₃, and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, purified by medium-pressure liquid chromatography (NH-silica gel, 25% EtOAc in hexane), and concentrated. To a solution of the residue in EtOAc (1 mL) was added 4 M hydrogen chloride in EtOAc (5 mL). The reaction mixture was stirred at ambient temperature for 30 min, and concentrated. A solution of the residue in Et₂O (10 mL) was stirred at ambient temperature for 1 hr and the precipitate was collected by filtration to give *cis*-N²-{4-[(4-bromo-2-trifluoromethoxy-benzylamino)-methyl]-cyclohexyl}-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride (147 mg, 34%) as a white solid.

ESI MS m/e 552, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.62 (s, 1 H), 10.07 (brs,

2 H), 8.66 (d, $J = 7.6$ Hz, 1 H), 8.22 (d, $J = 8.4$ Hz, 1 H), 7.90 (d, $J = 8.4$ Hz, 1 H), 7.65 (t, $J = 7.6$ Hz, 1 H), 7.52 (dd, $J = 8.3, 1.8$ Hz, 1 H), 7.33-7.48 (m, 2 H), 7.26 (t, $J = 7.5$ Hz, 1 H), 4.11-4.36 (m, 3 H), 3.51 (s, 6 H), 2.76-2.97 (m, 2 H), 1.51-2.27 (m, 9 H).

Example 42

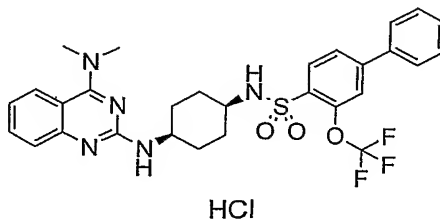


***cis*- N^4,N^4 -Dimethyl- N^2 -{4-[(2-trifluoromethoxy-benzylamino)-methyl]-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*- N^4,N^4 -dimethyl- N^2 -{4-[(2-trifluoromethoxy-benzylamino)-methyl]-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of example 41, the title compound was obtained. ESI MS m/e 474, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 12.81 (s, 1 H), 9.97 (brs, 1 H), 8.69 (d, $J = 7.5$ Hz, 1 H), 8.16-8.28 (m, 1 H), 7.90 (d, $J = 8.4$ Hz, 1 H), 7.63 (t, $J = 7.6$ Hz, 1 H), 7.18-7.51 (m, 4 H), 4.31 (brs, 2 H), 4.15-4.30 (m, 1 H), 3.50 (s, 6 H), 2.70-2.94 (m, 2 H), 1.41-2.28 (m, 10 H).

Example 43

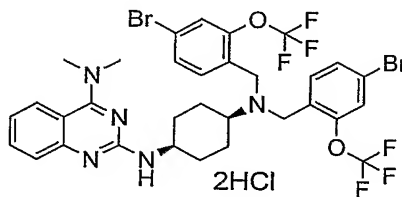


***cis*-3-Trifluoromethoxy-biphenyl-4-sulfonic acid [4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-amide hydrochloride**

Step A: Synthesis of *cis*-3-trifluoromethoxy-biphenyl-4-sulfonic acid [4-(4-

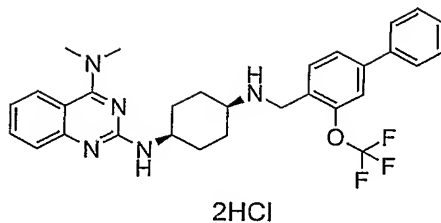
dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-amide hydrochloride.

Using the procedure for the step A of example 36, the title compound was obtained. ESI MS m/e 586, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 13.20 (brs, 1 H), 8.82 (d, J = 8.1 Hz, 1 H), 8.09 (d, J = 8.6 Hz, 1 H), 7.88 (d, J = 7.8 Hz, 1 H), 7.40-7.73 (m, 8 H), 7.25 (t, J = 8.4 Hz, 1 H), 5.41 (d, J = 8.6 Hz, 1 H), 4.07-4.22 (m, 1 H), 3.49 (s, 6 H), 3.37-3.62 (m, 1 H), 1.57-2.01 (m, 8 H).

Example 44***cis*- N^2 -{4-[Bis-(4-bromo-2-trifluoromethoxy-benzyl)-amino]-cyclohexyl}- N^4,N^4 -dimethyl-quinazoline-2,4-diamine dihydrochloride****Step A: Synthesis of *cis*- N^2 -{4-[bis-(4-bromo-2-trifluoromethoxy-benzyl)-amino]-cyclohexyl}- N^4,N^4 -dimethyl-quinazoline-2,4-diamine dihydrochloride.**

Using the procedure for the step B of example 37, the title compound was obtained.

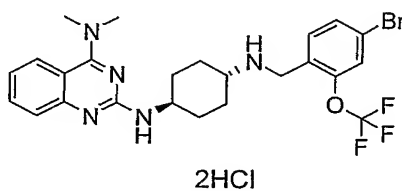
ESI MS m/e 790, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 12.50-12.82 (m, 2 H), 9.50-9.69 (m, 1 H), 8.39 (d, J = 8.1 Hz, 2 H), 7.91 (d, J = 8.1 Hz, 1 H), 7.66 (t, J = 7.8 Hz, 1 H), 7.48 (t, J = 8.7 Hz, 2 H), 7.07-7.43 (m, 4 H), 4.06-4.67 (m, 5 H), 3.51 (s, 6 H), 2.97-3.27 (m, 1 H), 2.21-2.59 (m, 4 H), 1.89-2.17 (m, 2 H), 1.36-1.82 (m, 2 H)

Example 45

***cis*-N⁴,N⁴-Dimethyl-N²-{4-[(3-trifluoromethoxy-biphenyl-4-yl)methyl]-amino}-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-N⁴,N⁴-dimethyl-N²-{4-[(3-trifluoromethoxy-biphenyl-4-yl)methyl]-amino}-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of example 43, the title compound was obtained. ESI MS *m/e* 536, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.63 (brs, 1 H), 10.07 (brs, 2 H), 8.68 (d, *J* = 7.3 Hz, 1 H), 8.33 (d, *J* = 8.1 Hz, 1 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 7.17-7.68 (m, 10 H), 4.40 (s, 2 H), 4.19-4.33 (m, 1 H), 3.50 (s, 6 H), 3.16-3.37 (m, 1 H), 2.03-2.48 (m, 6 H), 1.64-1.88 (m, 2 H).

Example 46

***trans*-N²-[4-(4-bromo-2-trifluoromethoxy-benzylamino)-cyclohexyl]-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

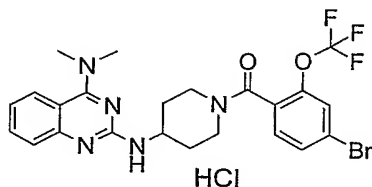
Step A: Synthesis of *trans*-N²-[4-(4-bromo-2-trifluoromethoxy-benzylamino)-cyclohexyl]-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS *m/e* 537, M (free)⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.00 (brs, 1 H), 10.08 (brs, 2 H), 8.40 (d, *J* = 7.2 Hz, 1 H), 8.05 (d, *J* = 8.2 Hz, 1 H), 7.91 (d, *J* = 8.4 Hz, 1 H), 7.65 (t,

$J = 7.7$ Hz, 1 H), 7.38-7.57 (m, 3 H), 7.26 (t, $J = 7.6$ Hz, 1 H), 4.17 (s, 2 H), 3.83-4.06 (m, 1 H), 3.53 (s, 6 H), 2.76-2.99 (m, 1 H), 2.09-2.46 (m, 4 H), 1.74-2.00 (m, 2 H), 1.28-1.58 (m, 2 H).

Example 47



1-(4-Bromo-2-trifluoromethoxy-phenyl)-1-[4-(4-dimethylamino-quinazolin-2-ylamino)-piperidin-1-yl]-methanone hydrochloride

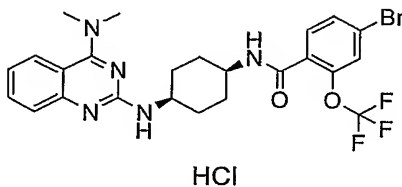
Step A: Synthesis of (4-bromo-2-trifluoromethoxy-phenyl)-[4-(4-dimethylamino-quinazolin-2-ylamino)-piperidin-1-yl]-methanone hydrochloride.

To a solution of 4-bromo-2-trifluoromethoxy-benzoic acid obtained in step B of example 13 (440 mg, 1.47 mmol) in CH_2Cl_2 (5 mL) were added DMF (1.1 μL , 15 μmol) and SOCl_2 (175 μL , 2.09 mmol). The mixture was stirred at reflux for 30 min and concentrated to give acid chloride as a pale yellow oil. To a solution of N,N' -dimethyl- N^2 -piperidin-4-yl-quinazoline-2,4-diamine obtained in step B of example 30 (400 mg, 1.47 mmol) in CH_2Cl_2 (4 mL) was added diisopropylethylamine (538 μL , 3.08 mmol). The mixture was cooled at 4 °C and a solution of above acid chloride in CH_2Cl_2 (3 mL) was added below 5 °C. The reaction mixture was stirred at 4 °C for 3 hr. The reaction was quenched with saturated aqueous NaHCO_3 , and the aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by flash chromatography (NH-silica gel, 25% EtOAc in hexane) to give a pale yellow oil. To a solution of above oil in EtOAc (1 mL) was added 4 M hydrogen chloride in EtOAc (0.26 mL). The mixture was stirred at ambient temperature for 50 min and concentrated. A solution of the residue in Et_2O (5 mL) was stirred at ambient temperature for 30 min. The precipitate was collected by filtration, washed with Et_2O , and dried under reduced pressure to give (4-bromo-2-trifluoromethoxy-phenyl)-[4-(4-dimethylamino-quinazolin-2-ylamino)-piperidin-1-yl]-methanone hydrochloride (126

mg, 16%) as a white solid.

ESI MS m/e 538, M (free) + H^+ ; 1H NMR (200 MHz, $CDCl_3$) δ 13.35 (brs, 1 H), 9.06 (d, $J = 7.5$ Hz, 1 H), 7.93 (d, $J = 8.4$ Hz, 1 H), 7.67 (dt, $J = 7.7, 0.9$ Hz, 1 H), 7.43-7.61 (m, 3 H), 7.18-7.41 (m, 2 H), 4.00-4.44 (m, 2 H), 3.54 (s, 6 H), 3.03-3.78 (m, 3 H), 1.52-2.24 (m, 4 H).

Example 48

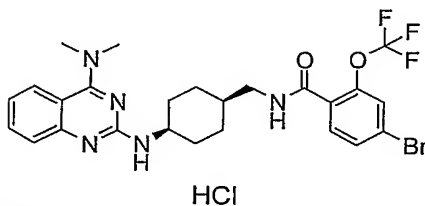


***cis*-4-Bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzamide dihydrochloride**

Step A: Synthesis of 4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzamide dihydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS m/e 551, M (free) $^+$; 1H NMR (200 MHz, $CDCl_3$) δ 13.24 (brs, 1 H), 8.95 (d, $J = 7.9$ Hz, 1 H), 7.92 (d, $J = 8.4$ Hz, 1 H), 7.71 (d, $J = 8.4$ Hz, 1 H), 7.60-7.67 (m, 1 H), 7.44-7.58 (m, 3 H), 7.20-7.34 (m, 1 H), 6.57 (d, $J = 8.4$ Hz, 1 H), 4.00-4.41 (m, 2 H), 3.53 (s, 6 H), 1.66-2.04 (m, 8 H).

Example 49

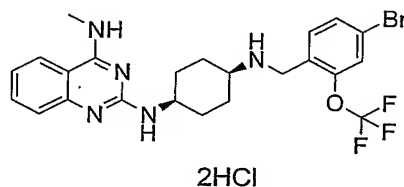


***cis*-4-Bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamide hydrochloride**

Step A: Synthesis of 4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamide hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 565, *M* (free)⁺; ¹H NMR (200 MHz, CDCl₃) δ 13.20 (brs, 1 H), 8.93 (d, *J* = 7.9 Hz, 1 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 1 H), 7.42-7.70 (m, 4 H), 7.18-7.34 (m, 1 H), 6.87 (t, *J* = 5.5 Hz, 1 H), 4.34 (brs, 1 H), 3.51 (s, 6 H), 3.43 (t, *J* = 5.7 Hz, 2 H), 1.52-2.17 (m, 9 H).

Example 50



***cis*-*N*²-[4-(4-Bromo-2-trifluoromethoxy-benzylamino)-cyclohexyl]-*N*⁴-methyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of (2-chloro-quinazolin-4-yl)-methyl-amine.

A solution of 2,4-dichloro-quinazoline obtained in step A of example 1 (125 g, 628 mmol) in THF (1 L) was cooled to 4 °C and 40% aqueous MeNH₂ (136 mL, 1.57 mol) was added. The mixture was stirred at ambient temperature for 80 min. The solution was alkalized with saturated aqueous NaHCO₃ (pH = 9) and concentrated. The precipitate was collected by filtration, washed with H₂O and hexane, and dried at 80 °C to give (2-chloro-quinazolin-4-yl)-methyl-amine (114 g, 94%) as a white solid.

ESI MS *m/e* 193, *M*⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.68-7.78 (m, 3 H), 7.39-7.48 (m, 1 H), 6.34 (brs, 1 H), 3.22 (d, *J* = 4.8 Hz, 3 H).

Step B: Synthesis of *cis*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester.

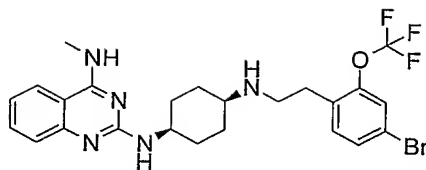
Using the procedure for the step G of example 1, the title compound was obtained. ESI MS *m/e* 372, *M* + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.56 (m, 3 H), 7.06 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H), 5.71 (brs, 1 H), 5.10 (brs, 1 H), 4.45-4.72 (m, 1 H), 4.00-4.26 (m,

1 H), 3.49-3.76 (m, 1 H), 3.12 (d, $J = 4.8$ Hz, 3 H), 1.50-1.93 (m, 8 H), 1.46 (s, 9 H).

Step C: Synthesis of *cis*- N^2 -[4-(4-bromo-2-trifluoromethoxy-benzylamino)-cyclohexyl]- N^4 -methyl-quinazoline-2,4-diamine dihydrochloride.

To a suspension of *cis*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (1.75 g, 4.71 mmol) in EtOAc (5 mL) and CHCl_3 (10 mL) was added 4 M hydrogen chloride in EtOAc (15 mL). The reaction mixture was stirred at ambient temperature for 2 hr, and concentrated. The residue was alkalized with saturated aqueous NaHCO_3 and the aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated (2.15 g). To a suspension of the above residue (300 mg, 1.11 mmol) in CH_2Cl_2 (3 mL) were added 4-bromo-2-trifluoromethoxy-benzaldehyde obtained in Step A of Example 13 (297 mg, 1.10 mmol), AcOH (66 mg, 1.10 mmol), and $\text{NaBH}(\text{OAc})_3$ (351 mg, 1.66 mmol). The reaction mixture was stirred at ambient temperature with CaCl_2 tube for 4 hr, poured into saturated aqueous NaHCO_3 , and the aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, purified by medium-pressure liquid chromatography (NH-silica gel, 50% EtOAc in hexane), and concentrated to give a pale yellow oil (91 mg). To a solution of the residue (71 mg) in EtOAc (1 mL) was added 4 M hydrogen chloride in EtOAc (5 mL). The reaction mixture was stirred at ambient temperature for 30 min, and concentrated. A solution of the residue in Et_2O (10 mL) was stirred at ambient temperature for 1 hr and the precipitate was collected by filtration to give *cis*- N^2 -[4-(4-bromo-2-trifluoromethoxy-benzylamino)-cyclohexyl]- N^4 -methyl-quinazoline-2,4-diamine dihydrochloride (62 mg, 20%) as a white solid.

ESI MS m/e 524, M (free) + H^+ ; ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.57 (m, 6 H), 7.05 (ddd, $J = 8.2, 6.8, 1.4$ Hz, 1 H), 5.52 (brs, 1 H), 4.09-4.27 (m, 1 H), 3.82 (s, 2 H), 3.12 (d, $J = 4.8$ Hz, 3 H), 2.57-2.72 (m, 1 H), 1.41-1.94 (m, 8 H).

Example 51

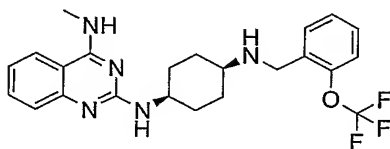
2HCl

***cis*-N²-{4-[2-(4-Bromo-2-trifluoromethoxy-phenyl)-ethylamino]-cyclohexyl}-N⁴-methyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-N²-{4-[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethylamino]-cyclohexyl}-N⁴-methyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step C of example 50, the title compound was obtained.

ESI MS *m/e* 538, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.18 (brs, 1 H), 9.93 (brs, 3 H), 8.74 (d, *J* = 6.2 Hz, 1 H), 7.71-7.94 (m, 1 H), 7.60 (t, 1 H, *J* = 7.7 Hz, 1 H), 7.21-7.45 (m, 5 H), 3.94-4.26 (m, 1 H), 3.35-3.58 (m, 2 H), 3.08-3.33 (m, 3 H), 2.94 (brs, 3 H), 1.64-2.42 (m, 8 H).

Example 52

2HCl

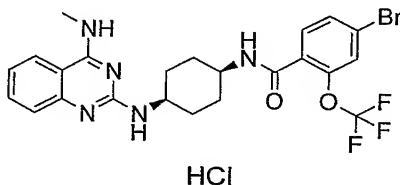
***cis*-N⁴-Methyl-N²-[4-(2-trifluoromethoxy-benzylamino)-cyclohexyl]-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-N⁴-methyl-N²-[4-(2-trifluoromethoxy-benzylamino)-cyclohexyl]-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step C of example 50, the title compound was obtained.

ESI MS m/e 446, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.56 (m, 4 H), 7.17-7.33 (m, 3 H), 7.04 (ddd, 1 H, $J = 8.2, 6.8, 1.4$ Hz, 1 H), 5.66 (brs, 1 H), 5.18 (brs, 1 H), 4.11-4.27 (m, 1 H), 3.87 (s, 2 H), 3.10 (d, $J = 4.8$ Hz, 3 H), 2.60-2.74 (m, 1 H), 1.45-1.95 (m, 8 H).

Example 53



cis-4-Bromo-*N*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzamide hydrochloride

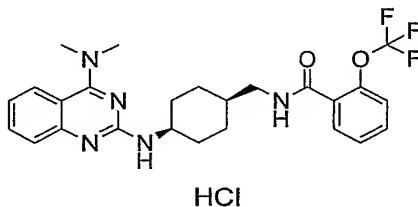
Step A: Synthesis of *cis*-4-bromo-*N*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzamide hydrochloride.

To a suspension of *cis*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester obtained in step B of example 50 (1.75 g, 4.71 mmol) in EtOAc (5 mL) and $CHCl_3$ (10 mL) was added 4 M hydrogen chloride in EtOAc (15 mL). The reaction mixture was stirred at ambient temperature for 2 hr, and concentrated. The residue was alkalized with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated. To a solution of 4-bromo-2-trifluoromethoxy-benzoic acid obtained in step B of example 13 (331 mg, 1.16 mmol) in CH_2Cl_2 (5 mL) were added DMF (1 μ L, 0.01 mmol) and $SOCl_2$ (120 μ L, 1.65 mmol). The mixture was stirred at reflux for 30 min and concentrated to give acid chloride as a pale yellow oil. To a suspension of *cis*-*N*-(4-amino-cyclohexyl)-*N*⁴-methyl-quinazoline-2,4-diamine (300 mg, 1.11 mmol) in CH_2Cl_2 (3 mL) was added diisopropylethylamine (410 μ L, 2.35 mmol). The mixture was cooled on an ice-bath and a solution of the above residue in CH_2Cl_2 (3 mL) was added dropwise. The reaction mixture was stirred on an ice-bath for 3.5 hr. The reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated, and purified by

flash chromatography (NH-silica gel, 50% EtOAc in hexane) to give a pale yellow solid. To a solution of the residue (116 mg) in EtOAc (1 mL) was added 4 M hydrogen chloride in EtOAc (5 mL). The reaction mixture was stirred at ambient temperature for 30 min, and concentrated. A solution of the residue in Et₂O (10 mL) was stirred at ambient temperature for 1 hr and the precipitate was collected by filtration to give 4-bromo-*N*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzamide (102 mg, 16%) as a white solid.

ESI MS *m/e* 538, *M* (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.72 (s, 1 H), 8.66 (d, *J* = 7.1 Hz, 1 H), 8.35 (brs, 1 H), 8.16 (d, *J* = 7.7 Hz, 1 H), 7.74 (d, *J* = 8.4 Hz, 1 H), 7.48-7.60 (m, 2 H), 7.40-7.43 (m, 1 H), 7.30 (d, *J* = 8.4 Hz, 1 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 6.57 (d, *J* = 8.1 Hz, 1 H), 4.34 (brs, 1 H), 4.15 (brs, 1 H), 3.22 (d, *J* = 3.9 Hz, 3 H), 1.90 (m, 8 H).

Example 54



***cis*-*N*-[4-(4-Dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamide hydrochloride**

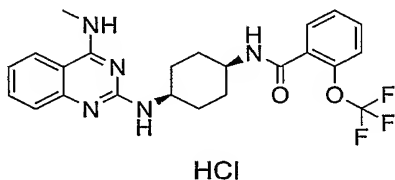
Step A: Synthesis of *cis*-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamide hydrochloride.

To a solution of *cis*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester obtained in step B of example 24 (4.57 g, 10.5 mmol) in MeOH (46 mL) was added 5% Pd/C (460 mg). The mixture was stirred at 50 °C under hydrogen atmosphere for 3 days, filtered, and concentrated to give a white solid (3.79 g). To a solution of the above solid (300 mg, 1.00 mmol) in CH₂Cl₂ (3 mL) was added triethylamine (280 μL, 2.01 mmol). The mixture was cooled on an ice-bath and a solution of 2-trifluoromethoxy-benzoyl chloride (236 mg, 1.05 mmol) in CH₂Cl₂ (2 mL) was added dropwise. The reaction mixture was stirred on an ice-bath for 5 hr. The reaction was quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered,

concentrated, purified by flash chromatography (NH-silica gel, 33% EtOAc in hexane and silica gel, 10% MeOH in CHCl_3), and concentrated. To a solution of the residue in EtOAc (1 mL) was added 4 M hydrogen chloride in EtOAc (5 mL). The reaction mixture was stirred at ambient temperature for 30 min, and concentrated. A solution of the residue in Et_2O (10 mL) was stirred at ambient temperature for 1 hr and the precipitate was collected by filtration to give *cis-N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamide hydrochloride (134 mg, 31%) as a white solid.

ESI MS m/e 510, M (free) + Na^+ ; ^1H NMR (300 MHz, CDCl_3) δ 13.29 (s, 1 H), 8.89 (d, $J = 7.9$ Hz, 1 H), 7.93 (dd, $J = 7.7, 1.8$ Hz, 1 H), 7.89 (d, $J = 8.4$ Hz, 1 H), 7.63 (t, $J = 7.3$ Hz, 1 H), 7.52 (d, $J = 7.9$ Hz, 1 H), 7.47 (dd, $J = 8.1, 1.9$ Hz, 1 H), 7.39 (t, $J = 7.6$ Hz, 1 H), 7.29 (d, $J = 9.0$ Hz, 1 H), 7.23 (d, $J = 7.3$ Hz, 1 H), 6.77 (t, $J = 5.6$ Hz, 1 H), 4.18-4.36 (m, 1 H), 3.51 (s, 6 H), 3.42 (t, $J = 6.3$ Hz, 2 H), 1.35-2.02 (m, 9 H).

Example 55

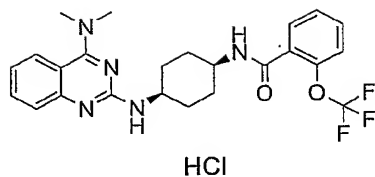


***cis-N*-[4-(4-Methylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzamide hydrochloride**

Step A: Synthesis of *cis-N*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzamide hydrochloride.

Using the procedure for the step A of example 54, the title compound was obtained. ESI MS m/e 460, M (free) + H^+ ; ^1H NMR (300 MHz, CDCl_3) δ 12.61 (s, 1 H), 8.70 (d, $J = 4.4$ Hz, 1 H), 8.57 (d, $J = 7.6$ Hz, 1 H), 8.26 (d, $J = 8.1$ Hz, 1 H), 7.82 (dd, $J = 7.7, 1.8$ Hz, 1 H), 7.08-7.57 (m, 6 H), 6.60 (d, $J = 8.1$ Hz, 1 H), 4.25-4.45 (m, 1 H), 4.01-4.25 (m, 1 H), 3.20 (d, $J = 4.5$ Hz, 3 H), 1.53-2.18 (m, 8 H).

Example 56



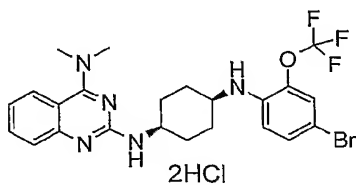
***cis*-N-[4-(4-Dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzamide hydrochloride**

Step A: Synthesis of *cis*-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzamide hydrochloride.

To a suspension of polymer supported DMAP (2.45 g, 7.35 mmol) in CH_2Cl_2 (6 mL) were added 2-trifluoromethoxy-benzoyl chloride (472 mg, 2.10 mmol) and *cis*-N²-(4-amino-cyclohexyl)-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine obtained in step C of example 9 (300 mg, 1.05 mmol). The mixture was stirred at ambient temperature for 24 h, filtered, poured into saturated aqueous NaHCO_3 . The aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, purified by medium-pressure liquid chromatography (NH-silica gel, 25% EtOAc in hexane), and concentrated. To a solution of the residue in EtOAc (1 mL) was added 4 M hydrogen chloride in EtOAc (10 mL). The reaction mixture was stirred at ambient temperature for 1 hr, and concentrated. A solution of the residue in Et_2O (10 mL) was stirred at ambient temperature for 1 hr and the precipitate was collected by filtration to give *cis*-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-trifluoromethoxy-benzamide hydrochloride (145 mg, 27%) as a white solid.

ESI MS m/e 474, $M + H^+$; ^1H NMR (300 MHz, CDCl_3) δ 13.22 (s, 1 H), 8.88 (d, $J = 7.5$ Hz, 1 H), 7.90 (d, $J = 8.2$ Hz, 1 H), 7.79 (dd, $J = 7.6, 1.9$ Hz, 1 H), 7.64 (t, $J = 7.5$ Hz, 1 H), 7.52 (d, $J = 8.7$ Hz, 1 H), 7.47 (dd, $J = 8.1, 1.9$ Hz, 1 H), 7.37 (dt, $J = 7.5, 1.2$ Hz, 1 H), 7.20-7.33 (m, 2 H), 6.66 (d, $J = 8.4$ Hz, 1 H), 4.06-4.36 (m, 2 H), 3.52 (s, 6 H), 1.55-2.21 (m, 8 H).

Example 57



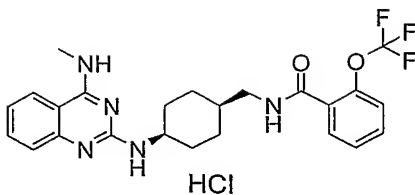
***cis*-*N*²-[4-(4-Bromo-2-trifluoromethoxy-phenylamino)-cyclohexyl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-*N*²-[4-(4-bromo-2-trifluoromethoxy-phenylamino)-cyclohexyl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

To a glass flask were added 18-crown-6 (647 mg, 2.45 mmol), 4-Bromo-1-iodo-2-trifluoromethoxy-benzene (770 mg, 2.10 mmol), *cis*-*N*²-(4-amino-cyclohexyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine obtained in step C of example 9 (500 mg, 1.75 mmol), sodium *tert*-butoxide (235 mg, 2.45 mmol), tris(dibenzylideneacetone)dipalladium (160 mg, 0.175 mmol), (R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (160 mg, 0.175 mmol) and THF (3.5 mL). The reaction mixture was stirred at reflux 18 hr. The mixture was filtered through a pad of celite, concentrated, and purified by flash chromatography (NH-silica gel, 33% EtOAc in hexane) to give a pale yellow oil. To a solution of above oil in Et₂O (2 mL) was added 4 M hydrogen chloride in EtOAc (0.3 mL). The mixture was stirred at ambient temperature for 30 min and concentrated. A solution of the residue in Et₂O (2 mL) was stirred at ambient temperature for 15 min. The precipitate was collected by filtration, washed with Et₂O, and dried under reduced pressure to give *cis*-*N*²-[4-(4-bromo-2-trifluoromethoxy-phenylamino)-cyclohexyl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride (189 mg, 18%) as a white solid.

ESI MS *m/e* 524, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.04 (s, 1 H), 8.85 (d, *J* = 7.9 Hz, 1 H), 7.90 (d, *J* = 8.1 Hz, 1 H), 7.61-7.70 (m, 1 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.22-7.31 (m, 1 H), 6.94 (s, 1 H), 6.79 (s, 1 H), 6.65 (s, 1 H), 4.28 (brs, 1H), 3.52 (s, 6 H), 3.30-3.45 (m, 2 H), 1.64-2.08 (m, 8 H).

Example 58



***cis*-N-[4-(4-Methylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamid hydrochloride**

Step A: Synthesis of *cis*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester.

Using the procedure for the step G of Example 1, the title compound was obtained. ESI MS *m/e* 420, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.20-7.59 (m, 8 H), 7.04 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H), 5.54-5.76 (m, 1 H), 5.10 (s, 2 H), 4.78-5.24 (m, 2 H), 4.18-4.36 (m, 1 H), 3.11 (d, *J* = 4.8 Hz, 3 H), 2.92-3.16 (m, 2 H), 1.06-1.94 (m, 9 H).

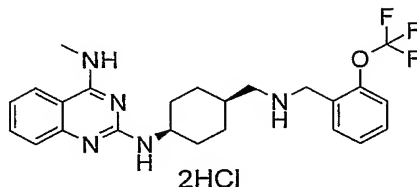
Step B: Synthesis of *cis*-N-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamid hydrochloride.

To a solution of *cis*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester (2.73 g, 6.50 mmol) in MeOH (27 mL) was added 10% Pd/C (273 mg). The mixture was stirred at 50 °C under hydrogen atmosphere for 14 hr, filtered, and concentrated to give a colorless solid (1.95 g). To a suspension of polymer supported DMAP (2.45 g, 7.35 mmol) in CH₂Cl₂ (10 mL) were added 2-trifluoromethoxy-benzoyl chloride (472 mg, 2.10 mmol) and the above solid (300 mg, 1.05 mmol). The mixture was stirred at ambient temperature for 2.5 days, filtered, poured into saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, purified by medium-pressure liquid chromatography (NH-silica gel, 50% EtOAc in hexane) and flash chromatography (silica gel, 20% MeOH in CHCl₃), and concentrated. To a solution of the residue in EtOAc (1 mL) was added 4 M hydrogen chloride in EtOAc (5 mL). The reaction mixture was stirred at ambient temperature for 30 min, and concentrated. A solution of the residue in Et₂O (5 mL) was stirred at ambient temperature for 1 hr and the precipitate was collected by filtration to give *cis*-N-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamide hydrochloride (20 mg, 4%) as a white solid.

ESI MS *m/e* 474, M + H⁺; ¹H NMR (500 MHz, CDCl₃) δ 12.82 (s, 1 H), 8.63 (d, *J* = 7.3

Hz, 1 H), 7.97-8.12 (m, 2 H), 7.91 (dd, $J = 7.6, 1.5$ Hz, 1 H), 7.54 (t, $J = 7.6$ Hz, 1 H), 7.48 (dt, $J = 7.9, 1.8$ Hz, 1 H), 7.38 (t, $J = 7.0$ Hz, 1 H), 7.26-7.35 (m, 2 H), 7.19 (t, $J = 7.6$ Hz, 1 H), 6.77 (t, $J = 5.8$ Hz, 1 H), 4.30-4.41 (m, 1 H), 3.41 (t, $J = 6.4$ Hz, 2 H), 3.20 (d, $J = 3.7$ Hz, 3 H), 1.48-2.01 (m, 9 H).

Example 59



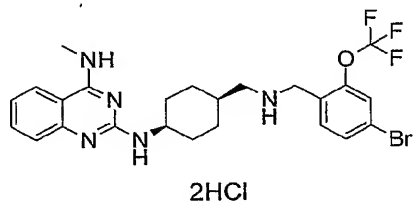
***cis*-N⁴-Methyl-N²-{4-[(2-trifluoromethoxy-benzylamino)-methyl]-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-N⁴-methyl-N²-{4-[(2-trifluoromethoxy-benzylamino)-methyl]-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride.

To a solution of *cis*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester obtained in step A of example 58 (2.73 g, 6.50 mmol) in MeOH (27 mL) was added 10% Pd/C (273 mg). The mixture was stirred at 50 °C under hydrogen atmosphere for 14 hr, filtered, and concentrated to give a colorless solid (1.95 g). To a solution of the above solid (300 mg, 1.05 mmol) in MeOH (3 mL) were added 2-trifluoromethoxy-benzaldehyde (200 mg, 1.05 mmol), AcOH (63 mg, 1.05 mmol), and NaBH₃CN (99 mg, 1.58 mmol). The reaction mixture was stirred at ambient temperature with CaCl₂ tube for 4 hr, poured into 1 M aqueous sodium hydroxide, and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, purified by medium-pressure liquid chromatography (NH-silica gel, 50% EtOAc in hexane) and flash chromatography (silica gel, 10% MeOH in CHCl₃), and concentrated. To a solution of the residue in EtOAc (1 mL) was added 4 M hydrogen chloride in EtOAc (5 mL). The reaction mixture was stirred at ambient temperature for 30 min, and concentrated. A solution of the residue in Et₂O (10 mL) was stirred at ambient temperature for 1 hr and the precipitate was collected by filtration to give *cis*-N⁴-methyl-N²-{4-[(2-trifluoromethoxy-benzylamino)-methyl]-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride (175 mg, 33%) as a white solid.

ESI MS m/e 460, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 11.49 (brs, 1 H), 9.74 (brs, 1 H), 9.57 (d, $J = 4.4$ Hz, 1 H), 8.43 (d, $J = 8.4$ Hz, 1 H), 8.27 (d, $J = 8.4$ Hz, 1 H), 8.13 (dd, $J = 7.5, 1.8$ Hz, 1 H), 7.24-7.51 (m, 4 H), 6.95-7.16 (m, 2 H), 4.28 (s, 2 H), 4.13-4.38 (m, 1 H), 2.99 (d, $J = 4.5$ Hz, 3 H), 2.92 (d, $J = 4.8$ Hz, 2 H), 1.41-2.19 (m, 9 H).

Example 60



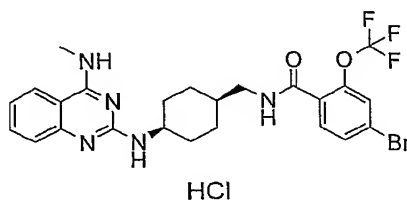
cis-N²-{4-[(4-Bromo-2-trifluoromethoxy-benzylamino)-methyl]-cyclohexyl}-*N⁴*-methyl-quinazoline-2,4-diamine dihydrochloride

Step A: Synthesis of *cis-N²*-{4-[(4-bromo-2-trifluoromethoxy-benzylamino)-methyl]-cyclohexyl}-*N⁴*-methyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of Example 59, the title compound was obtained.

ESI MS m/e 538, M (free) + H^+ ; 1H NMR (500 MHz, $CDCl_3$) δ 11.23 (brs, 1 H), 9.75 (brs, 2 H), 9.46 (brs, 1 H), 8.43 (d, $J = 7.9$ Hz, 1 H), 8.29 (d, $J = 8.5$ Hz, 1 H), 8.08 (d, $J = 8.5$ Hz, 1 H), 7.55 (dd, $J = 8.6, 1.8$ Hz, 1 H), 7.44-7.52 (m, 2 H), 7.14 (t, $J = 7.3$ Hz, 1 H), 7.07 (d, $J = 7.9$ Hz, 1 H), 4.24 (s, 2 H), 4.19-4.30 (m, 1 H), 2.88-3.05 (m, 5 H), 1.38-1.84 (m, 9 H).

Example 61



***cis*-4-Bromo-*N*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamide hydrochloride**

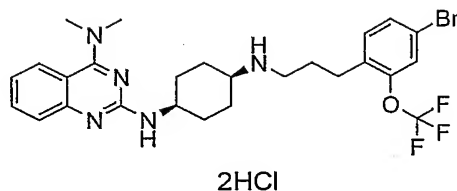
Step A: Synthesis of *cis*-4-bromo-*N*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamide hydrochloride.

To a solution of *cis*-[4-(4-Methylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester obtained in step A of example 58 (2.73 g, 6.50 mmol) in MeOH (27 mL) was added 10% Pd/C (273 mg). The mixture was stirred at 50 °C under hydrogen atmosphere for 14 hr, filtered, and concentrated to give *cis*-*N*²-(4-Aminomethyl-cyclohexyl)-*N*⁴-methyl-quinazoline-2,4-diamine (1.95 g) as a white solid. To a solution of 4-bromo-2-trifluoromethoxy-benzoic acid obtained in step B of example 13 (599 mg, 2.10 mmol) in CH₂Cl₂ (6 mL) was added DMF (1 μL, 14.7 μmol) and SOCl₂ (190 μL, 2.60 mmol). The mixture was stirred at reflux for 30 min and concentrated to give acid chloride as a pale yellow oil. To a suspension of polymer supported DMAP (2.45 g, 7.35 mmol) in CH₂Cl₂ (6 mL) were added above acid chloride and *cis*-*N*²-(4-aminomethyl-cyclohexyl)-*N*⁴-methyl-quinazoline-2,4-diamine (300 mg). The mixture was stirred at ambient temperature for 24 hr, filtered, poured into saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, purified by medium-pressure liquid chromatography (NH-silica gel, 50% EtOAc in hexane), and concentrated. To a solution of the residue in EtOAc (1 mL) was added 4 M hydrogen chloride in EtOAc (10 mL). The reaction mixture was stirred at ambient temperature for 1 hr, and concentrated. A solution of the residue in Et₂O (10 mL) was stirred at ambient temperature for 1 hr and the precipitate was collected by filtration to give *cis*-4-bromo-*N*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamide hydrochloride (47 mg, 8%) as a white solid.

ESI MS *m/e* 551, *M* (free)⁺; ¹H NMR (500 MHz, CDCl₃) δ 12.61 (s, 1 H), 8.56 (d, *J* = 7.3 Hz, 1 H), 8.40 (brs, 1 H), 8.15 (d, *J* = 8.5 Hz, 1 H), 7.78 (d, *J* = 8.5 Hz, 1 H), 7.47-7.55 (m, 2 H), 7.42 (t, *J* = 1.5 Hz, 1 H), 7.26 (d, *J* = 8.5 Hz, 1 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 6.88 (t, *J*

= 5.8 Hz, 1 H), 4.32-4.44 (m, 1 H), 3.40 (t, J = 6.1 Hz, 2 H), 3.20 (d, J = 4.3 Hz, 3 H), 1.49-2.00 (m, 8 H).

Example 62



***cis*-N²-{4-[3-(4-Bromo-2-trifluoromethoxy-phenyl)-propylamino]-cyclohexyl}-N,N'-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of (E)-3-(4-bromo-2-trifluoromethoxy-phenyl)-acrylic acid ethyl ester.

To a solution of (ethoxy-methoxymethyl-phosphinoyl)-acetic acid ethyl ester (3.45 g, 15.4 mmol) in THF (230 mL) was added 60% sodium hydride in oil (370 mg, 15.4 mmol). The mixture was stirred at ambient temperature for 50 min and cooled at 4 °C. To the reaction mixture was added 4-bromo-2-trifluoromethoxy-benzaldehyde (3 g, 11.2 mmol) in THF (100 mL). The mixture was stirred at ambient temperature for 15 hr. The solution was poured into H₂O, and the aqueous layer was extracted with EtOAc (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (silica gel, 5% EtOAc in hexane) to give (E)-3-(4-Bromo-2-trifluoromethoxy-phenyl)-acrylic acid ethyl ester (2.98 g, 79 %) as a colorless oil.

CI MS m/e 339, $M + H^+$; ¹H NMR (300 MHz, CDCl₃) δ 7.85 (d, J = 15.8 Hz, 1 H), 7.42-7.58 (m, 3 H), 6.48 (d, J = 15.8 Hz, 1 H), 4.29 (q, J = 7.0 Hz, 2 H), 1.35 (t, J = 7.0 Hz, 3 H).

Step B: Synthesis of 3-(4-bromo-2-trifluoromethoxy-phenyl)-propan-1-ol.

A suspension of lithium aluminum hydride (834 mg, 22.0 mmol) in Et₂O (20 mL) was cooled at 4 °C. A solution of (E)-3-(4-bromo-2-trifluoromethoxy-phenyl)-acrylic acid ethyl ester (2.98 g, 8.79 mmol) in Et₂O (9 mL) was added dropwise, and the mixture was

stirred at ambient temperature for 90 min. The reaction was quenched with EtOAc (6 mL) and saturated aqueous NH_4Cl was added dropwise. The aqueous layer was extracted with EtOAc (three times). The combined organic layer was washed with 1 M aqueous HCl, dried over MgSO_4 , filtered, concentrated, and purified by flash chromatography (silica gel, 25% EtOAc in hexane) to give 3-(4-bromo-2-trifluoromethoxy-phenyl)-propan-1-ol (1.14 g, 43 %) as a colorless oil.

EI MS m/e 298, M^+ ; ^1H NMR (300 MHz, CDCl_3) δ 7.10-7.43 (m, 3 H), 3.68 (t, J = 6.4 Hz, 2 H), 2.67-2.80 (m, 2 H), 1.75-1.94 (m, 2 H).

Step C: Synthesis of 3-(4-bromo-2-trifluoromethoxy-phenyl)-propionaldehyde.

A solution of 3-(4-bromo-2-trifluoromethoxy-phenyl)-propan-1-ol (1.03 g, 3.44 mmol) in CH_2Cl_2 (47 mL) was cooled at 4 °C and added celite (1.4 g) and pyridinium chlorochromate (1.11 g, 5.16 mmol). The reaction mixture was stirred at ambient temperature for 6 hr and filtered through a pad of celite, concentrated, and purified by flash chromatography (silica gel, 16% EtOAc in hexane) to give 3-(4-bromo-2-trifluoromethoxy-phenyl)-propionaldehyde (659 mg, 64%) as a colorless oil.

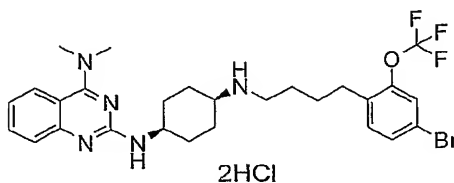
CI MS m/e 297, $\text{M} + \text{H}^+$; ^1H NMR (300 MHz, CDCl_3) δ 9.80 (t, J = 1.1 Hz, 1 H), 7.32-7.42 (m, 2 H), 7.17 (d, J = 8.4, Hz, 1 H), 2.96 (t, J = 7.4 Hz, 2 H), 2.72-2.81 (m, 2 H).

Step D: Synthesis of *cis*- N^2 -{4-[3-(4-bromo-2-trifluoromethoxy-phenyl)-propylamino]-cyclohexyl}- N^4 , N^4 -dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS m/e 566, M (free) + H^+ ; ^1H NMR (300 MHz, CDCl_3) δ 8.81 (d, J = 7.2 Hz, 1 H), 7.91 (d, J = 7.9 Hz, 1 H), 7.60-7.70 (m, 1 H), 7.49 (d, J = 8.4 Hz, 1 H), 7.12-7.42 (m, 5 H), 4.31 (brs, 1 H), 3.52 (s, 6 H), 3.23 (brs, 1 H), 3.02-3.14 (m, 2 H), 2.78 (t, J = 7.8 Hz, 2 H), 1.97-2.36 (m, 8 H), 1.59-1.85 (m, 2 H).

Example 63



***cis*-*N*²-{4-[4-(4-bromo-2-trifluoromethoxy-phenyl)-butylamino]-cyclohexyl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of (E)-4-(4-bromo-2-trifluoromethoxy-phenyl)-but-2-enoic acid ethyl ester.

Using the procedure for the step A of example 62, the title compound was obtained. ESI MS *m/e* 352, *M*⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.53 (m, 3 H), 6.64 (d, *J* = 16.2 Hz, 1 H), 6.37 (dt, *J* = 16.0, 7.1 Hz, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 3.28 (dd, *J* = 7.1, 1.5 Hz, 2 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

Step B: Synthesis of 4-(4-bromo-2-trifluoromethoxy-phenyl)-butan-1-ol.

Using the procedure for the step B of example 62, the title compound was obtained.

EI MS *m/e* 312, *M*⁺; ¹H NMR (200 MHz, CDCl₃) δ 7.10-7.42 (m, 3 H), 3.68 (t, *J* = 5.1 Hz, 2 H), 2.60-2.82 (m, 2 H), 1.50-1.79 (m, 4 H), 1.10-1.50 (brs, 1 H).

Step C: Synthesis of 4-(4-bromo-2-trifluoromethoxy-phenyl)-butyraldehyde.

Using the procedure for the step C of example 62, the title compound was obtained.

ESI MS *m/e* 311, *M* + *H*⁺; ¹H NMR (200 MHz, CDCl₃) δ 9.79 (s, 1 H), 7.02-7.22 (m, 3 H), 2.60-2.84 (m, 2 H), 2.49 (t, *J* = 5.9 Hz, 2 H), 1.80-2.03 (m, 2 H).

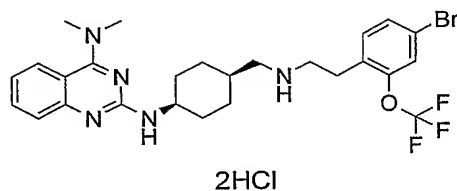
Step D: Synthesis of *cis*-*N*²-{4-[4-(4-bromo-2-trifluoromethoxy-phenyl)-butylamino]-cyclohexyl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

To a suspension of *cis*-*N*²-(4-amino-cyclohexyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine obtained in step C of example 9 (240 mg, 0.84 mmol) in MeOH (3 mL) were added 4-(4-bromo-2-trifluoromethoxy-phenyl)-butyraldehyde (262 mg, 0.84 mmol), acetic acid (79 mg, 1.26 mmol), and NaBH₃CN (79 mg, 1.26 mmol). The reaction mixture was

stirred at ambient temperature for 8 hr. The reaction was quenched with saturated aqueous NaHCO_3 . The aqueous layer was extracted with CHCl_3 (three times). The combined organic layer was dried over MgSO_4 , filtered, concentrated, and purified by medium-pressure liquid chromatography (NH-silica gel, 50% EtOAc in hexane) to give a pale yellow solid. To a solution of above solid in EtOAc (2 mL) was added 4 M hydrogen chloride in EtOAc (10 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated. A solution of the residue in Et_2O (20 mL) was stirred at ambient temperature for 1 hr. The solid was collected by filtration, washed with Et_2O , and dried under reduced pressure to give *cis*- N^2 -{4-[4-(4-bromo-2-trifluoromethoxy-phenyl)-butylamino]-cyclohexyl}- N^1,N^4 -dimethyl-quinazoline-2,4-diamine dihydrochloride (220 mg, 40%) as a white solid.

ESI MS m/e 580, M (free) + H^+ ; ^1H NMR (200 MHz, CDCl_3) δ 12.73 (brs, 1 H), 9.55 (brs, 2 H), 8.66-8.88 (m, 1 H), 7.92 (d, $J = 7.9$ Hz, 1 H), 7.66 (t, $J = 7.3$ Hz, 1 H), 7.48 (d, $J = 7.7$ Hz, 1 H), 7.12-7.40 (m, 3 H), 4.20-4.42 (m, 1 H), 3.52 (s, 6 H), 2.92-3.42 (m, 3 H), 2.60-2.78 (m, 2 H), 1.58-2.59 (m, 12 H).

Example 64



cis- N^2 -(4-{[2-(4-Bromo-2-trifluoromethoxy-phenyl)-ethylamino]-methyl}-cyclohexyl)- N^1,N^4 -dimethyl-quinazoline-2,4-diamine dihydrochloride

Step A: Synthesis of N^2 -(4-aminomethyl-cyclohexyl)- N^1,N^4 -dimethyl-quinazoline-2,4-diamine.

To a solution of *cis*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester obtained in step B of example 24 (12.1 g, 27.9 mmol) in MeOH (120 mL) was added 10% Pd/C (1.21 g). The mixture was stirred at 50 °C under hydrogen atmosphere for 19 hr, filtered, concentrated, and purified by flash

chromatography (NH-silica gel, 66% EtOAc in hexane to 15% MeOH in chloroform) to give *N*²-(4-aminomethyl-cyclohexyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine (6.9 g, 83%) as a yellow solid.

CI MS *m/e* 300, *M* + *H*⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (d, *J* = 8.4 Hz, 1 H), 7.40-7.51 (m, 2 H), 6.98-7.04 (m, 1 H), 5.04 (d, *J* = 7.3 Hz, 1 H), 4.24-4.30 (m, 1 H), 3.27 (s, 6 H), 2.60 (d, *J* = 6.4 Hz, 2 H), 1.81-1.96 (m, 2 H), 1.57-1.76 (m, 4 H), 0.90-1.51 (m, 5 H).

Step B: Synthesis of *cis-N*²-(4-{[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethylamino]-methyl}-cyclohexyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS *m/e* 566, *M* (free) + *H*⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.45 (s, 1 H), 9.74 (brs, 2 H), 8.70 (d, *J* = 7.6 Hz, 1 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.17-7.52 (m, 4 H), 4.30 (brs, 1 H), 3.52 (s, 6 H), 3.32-3.50 (m, 2 H), 3.17 (brs, 2 H), 3.01 (brs, 2 H), 1.56-2.10 (m, 9 H).

Example 65

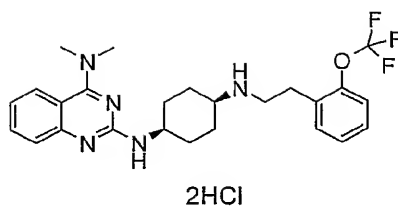


***cis-N*²-(4-{[2-(4-Bromo-2-trifluoromethoxy-phenyl)-ethylamino]-methyl}-cyclohexyl)-*N*⁴-methyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis-N*²-(4-{[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethylamino]-methyl}-cyclohexyl)-*N*⁴-methyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of example 59, the title compound was obtained.

ESI MS *m/e* 552 *M* (free) + *H*⁺; ¹H NMR (300 MHz, CDCl₃) δ 11.66 (s, 1 H), 9.62 (brs, 1 H), 9.40 (brs, 1 H), 8.05-8.50 (m, 2 H), 7.21-7.58 (m, 4 H), 6.96-7.21 (m, 2 H), 4.26 (brs, 1 H), 3.41 (brs, 2 H), 2.75-3.31 (m, 7H), 1.30-2.24 (m, 9 H).

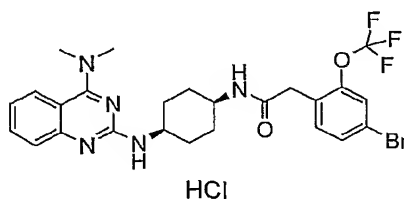
Example 66

***cis*-N',N'-Dimethyl-N²-{4-[2-(2-trifluoromethoxy-phenyl)-ethylamino]-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-N',N'-dimethyl-N²-{4-[2-(2-trifluoromethoxy-phenyl)-ethylamino]-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride.

To a solution of *cis*-N²-{4-[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethylamino]-cyclohexyl}-N',N'-dimethyl-quinazoline-2,4-diamine dihydrochloride obtained in step B of example 37 (250 mg, 0.4 mmol) in EtOH (5 mL) was added 10% Pd/C (75 mg). The mixture was stirred at ambient temperature under hydrogen atmosphere for 17 hr, filtered, poured into saturated aqueous NaHCO₃. The aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 50% EtOAc in hexane) to give a colorless oil. To a solution of above oil in EtOAc (4 mL) was added 4 M hydrogen chloride in EtOAc (0.25 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated. The residue was suspended with Et₂O (15 mL) and stirred at ambient temperature for 1 hr. The solid was collected by filtration, washed with Et₂O, and dried under reduced pressure to give *cis*-N',N'-dimethyl-N²-{4-[2-(2-trifluoromethoxy-phenyl)-ethylamino]-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride (104 mg, 48%) as a white solid.

ESI MS *m/e* 474, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.62 (s, 1 H), 9.78 (brs, 2 H), 8.71 (brs, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 7.39-7.77 (m, 3 H), 7.14-7.37 (m, 4 H), 4.33 (brs, 1 H), 3.15-3.71 (m, 11 H), 1.93-2.53 (m, 6 H), 1.62-1.89 (m, 2 H).

Example 67

***cis*-2-(4-Bromo-2-trifluoromethoxy-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-acetamide hydrochloride**

Step A: Synthesis of (4-bromo-2-trifluoromethoxy-phenyl)-acetic acid.

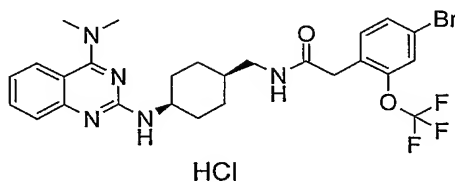
Using the procedure for the step B of example 13, the title compound was obtained.

ESI MS m/e 298, M^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.47 (m, 2 H), 7.22 (d, $J = 8.1$ Hz, 1 H), 3.70 (s, 2 H).

Step B: Synthesis of *cis*-2-(4-bromo-2-trifluoromethoxy-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-acetamide hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS m/e 566, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 13.15 (s, 1 H), 8.91 (d, $J = 7.7$ Hz, 1 H), 7.89 (d, $J = 8.4$ Hz, 1 H), 7.61-7.70 (m, 1 H), 7.48-7.56 (m, 1 H), 7.39-7.45 (m, 1 H), 7.21-7.33 (m, 2 H), 6.02 (d, $J = 8.8$ Hz, 1 H), 4.19-4.33 (m, 1 H), 3.82-4.03 (m, 1 H), 3.53 (s, 2 H), 3.51 (s, 6 H), 1.64-1.97 (m, 8 H).

Example 68



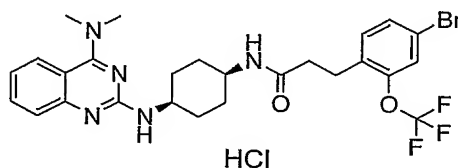
***cis*-2-(4-Bromo-2-trifluoromethoxy-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide hydrochloride**

Step A: Synthesis of *cis*-2-(4-bromo-2-trifluoromethoxy-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained.

ESI MS m/e 580, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 12.85 (brs, 1 H), 9.08 (d, J = 8.4 Hz, 1 H), 7.90 (d, J = 8.8 Hz, 1 H), 7.58-7.72 (m, 1 H), 7.19-7.54 (m, 5 H), 6.81-6.98 (m, 1 H), 4.28-4.51 (m, 1 H), 3.83 (s, 2 H), 3.51 (s, 6 H), 3.29-3.34 (m, 2 H), 1.42-2.03 (m, 9 H).

Example 69



***cis*-3-(4-Bromo-2-trifluoromethoxy-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)cyclohexyl]-propionamide hydrochloride**

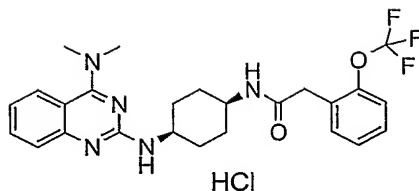
Step A: Synthesis of 3-(4-bromo-2-trifluoromethoxy-phenyl)-propionic acid.

To a solution of 3-(4-bromo-2-trifluoromethoxy-phenyl)-propan-1-ol obtained in step B of example 62 (1 g, 3.34 mmol) in acetone (15 mL) was added Jones reagent (4 mL) at 4 °C. The mixture was stirred at ambient temperature for 2 hr. The solution was poured into water (50 mL), and the aqueous layer was extracted with Et_2O (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (silica gel, 25% $EtOAc$ in hexane) to give 3-(4-Bromo-2-trifluoromethoxy-phenyl)-propionic acid (930 mg, 89%) as a colorless oil.

ESI MS m/e 313, M^+ ; 1H NMR (200 MHz, $CDCl_3$) δ 7.31-7.50 (m, 2 H), 7.10-7.29 (m, 1 H), 2.97 (t, J = 7.7 Hz, 2 H), 2.65 (t, J = 7.7 Hz, 2 H).

Step B: Synthesis of *cis*-3-(4-bromo-2-trifluoromethoxy-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)cyclohexyl]-propionamide hydrochloride.

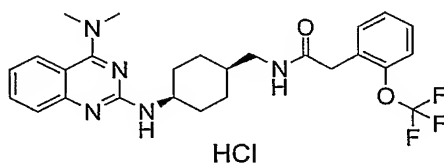
Using the procedure for the step A of example 47, the title compound was obtained. ESI MS m/e 580, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 13.12 (brs, 1 H), 8.92 (d, J = 7.9 Hz, 1 H), 7.90 (d, J = 8.3 Hz, 1 H), 7.47-7.73 (m, 2 H), 7.15-7.44 (m, 3 H), 5.92 (d, J = 8.4 Hz, 1 H), 4.18-4.38 (m, 1 H), 3.76-4.03 (m, 1 H), 3.51 (s, 6 H), 2.98 (t, J = 7.7 Hz, 2 H), 2.44 (t, J = 7.7 Hz, 2 H), 1.55-1.96 (m, 9 H).

Example 70

***cis*-N-[4-(4-Dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-(2-trifluoromethoxy-phenyl)-acetamide hydrochloride**

Step A: Synthesis of *cis*-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-2-(2-trifluoromethoxy-phenyl)-acetamide hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 488, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.20 (s, 1H), 8.84 (d, *J* = 7.6 Hz, 1 H), 7.89 (d, *J* = 8.7 Hz, 1 H), 7.60-7.70 (m, 1 H), 7.49-7.56 (m, 1 H), 7.20-7.43 (m, 5 H), 5.98 (d, *J* = 7.6 Hz, 1 H), 4.23 (brs, 1 H), 3.84-4.03 (m, 1 H), 3.59 (s, 2 H), 3.50 (s, 6 H), 1.62-1.98 (m, 8 H).

Example 71

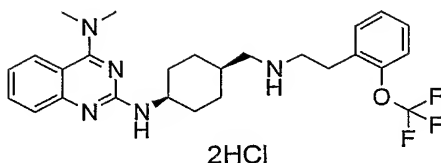
***cis*-N-[4-(4-Dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-(2-trifluoromethoxy-phenyl)-acetamide hydrochloride**

Step A: Synthesis of *cis*-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-(2-trifluoromethoxy-phenyl)-acetamide hydrochloride

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 502, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.99 (s, 1 H), 8.99 (d, *J* = 8.5 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 1 H), 7.63 (t, *J* = 7.62 Hz, 1 H), 7.38-7.54 (m, 2 H), 7.16-

7.34 (m, 4 H), 6.55 (brs, 1 H), 4.28-4.43 (m, 1 H), 3.81 (s, 2 H), 3.51 (s, 6 H), 3.27 (s, 2 H), 1.46-1.99 (m, 9 H).

Example 72

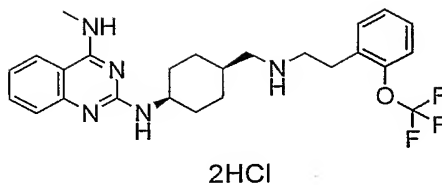


***cis-N⁴,N⁴*-Dimethyl-*N*²-(4-{[2-(2-trifluoromethoxy-phenyl)-ethylamino]-methyl}-cyclohexyl)-quinazoline-2,4-diamine dihydrochloride**

Step A: *cis-N⁴,N⁴*-dimethyl-*N*²-(4-{[2-(2-trifluoromethoxy-phenyl)-ethylamino]-methyl}-cyclohexyl)-quinazoline-2,4-diamine dihydrochloride

To a solution of *cis-N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-(2-trifluoromethoxy-phenyl)-acetamide (free) obtained in step A of example 71 (246 mg, 0.5 mmol) in THF (3.5 mL) was added 1 M borane-THF complex (2.45 mL, 2.45 mmol). The mixture was stirred at reflux for 2.5 h, and concentrated. To a solution of above residue in THF (3.5 mL) was added 1 M hydrochloric acid (4.41 mL, 4.41 mmol). The mixture was stirred at reflux for 1 hr, and cooled to ambient temperature. To the reaction mixture was added 2 M aqueous sodium hydroxide, and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by medium-pressure liquid chromatography (NH-silica gel, 50% EtOAc in hexane) to give a colorless oil. To a solution of above oil in EtOAc (4 mL) was added 4 M hydrogen chloride in EtOAc (0.25 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated. A solution of the residue in Et₂O (15 mL) was stirred at ambient temperature for 1 hr. The precipitate was collected by filtration, washed with Et₂O, and dried under reduced pressure to give *cis-N⁴,N⁴*-dimethyl-*N*²-{4-[2-(2-trifluoromethoxy-phenyl)-ethylamino]-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride (81 mg, 30%) as a white solid.

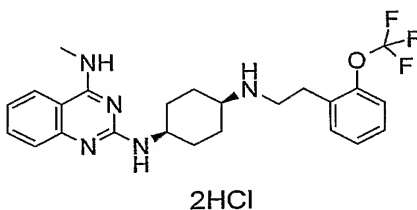
FAB MS *m/e* 488, *M* + *H*⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.56 (s, 1 H), 9.72 (brs, 1 H), 8.72 (d, *J* = 7.7 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 1 H), 7.66 (t, *J* = 7.7 Hz, 1 H), 7.42-7.54 (m, 2 H), 7.15-7.32 (m, 4 H), 4.22-4.35 (m, 1 H), 3.51 (s, 6 H), 3.38-3.59 (m, 2 H), 3.11-3.30 (m, 2 H), 2.92-3.07 (m, 2 H), 2.21 (brs, 1 H), 1.50-2.01 (m, 8 H).

Example 73

***cis-N⁴*-Methyl-*N²*-(4-{[2-(2-trifluoromethoxy-phenyl)-ethylamino]-methyl}-cyclohexyl)-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis-N⁴*-methyl-*N²*-(4-{[2-(2-trifluoromethoxy-phenyl)-ethylamino]-methyl}-cyclohexyl)-quinazoline-2,4-diamine dihydrochloride.

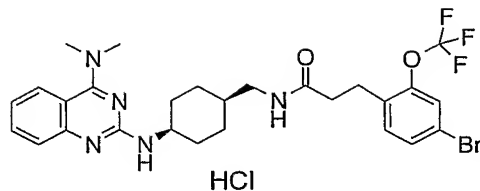
Using the procedure for the step A of example 66, the title compound was obtained. ESI MS *m/e* 474, M (free) + H⁺; ¹H NMR (200 MHz, CDCl₃) δ 11.72 (s, 1 H), 9.23-9.94 (m, 3 H), 8.00-8.66 (m, 2 H), 6.64-7.66 (m, 7 H), 4.26 (brs, 1 H), 2.73-3.65 (m, 9 H), 1.27-2.44 (m, 9 H).

Example 74

***cis-N⁴*-Methyl-*N²*-{4-[2-(2-trifluoromethoxy-phenyl)-ethylamino]-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis-N⁴*-methyl-*N²*-{4-[2-(2-trifluoromethoxy-phenyl)-ethylamino]-cyclohexyl}-quinazoline-2,4-diamine dihydrochloride.

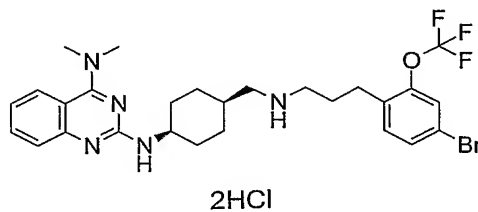
Using the procedure for the step A of example 66, the title compound was obtained. ESI MS *m/e* 460, M (free) + H⁺; ¹H NMR (200 MHz, CDCl₃) δ 12.20 (brs, 1 H), 9.84 (brs, 3 H), 8.59-8.79 (m, 1 H), 7.79-8.02 (m, 1 H), 7.10-7.70 (m, 7 H), 3.95-4.26 (m, 1 H), 3.09-3.54 (m, 5 H), 2.82-3.03 (m, 3 H), 1.57-2.43 (m, 8 H).

Example 75

***cis*-3-(4-Bromo-2-trifluoromethoxy-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-propionamide hydrochloride**

Step A: Synthesis of *cis*-3-(4-bromo-2-trifluoromethoxy-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-propionamide hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 594, *M* (free)⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.72 (s, 1 H), 9.01 (d, *J* = 8.7 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.47 (d, *J* = 7.6 Hz, 1 H), 7.21-7.41 (m, 3 H), 6.96 (brs, 1 H), 4.31-4.44 (m, 1 H), 3.51 (s, 6 H), 3.23-3.35 (m, 2 H), 3.03 (t, *J* = 7.6 Hz, 2 H), 2.76 (t, *J* = 7.6 Hz, 2 H), 1.38-1.98 (m, 9 H).

Example 76

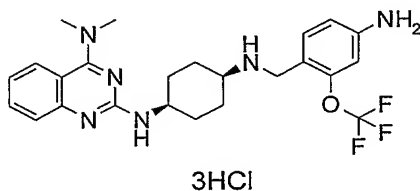
***cis*-*N*²-(4-{[3-(4-Bromo-2-trifluoromethoxy-phenyl)-propylamino]-methyl}-cyclohexyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-*N*²-(4-{[3-(4-bromo-2-trifluoromethoxy-phenyl)-propylamino]-methyl}-cyclohexyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of example 72, the title compound was obtained.

ESI MS m/e 580, M (free) + H^+ ; 1H NMR (200 MHz, $CDCl_3$) δ 12.56 (s, 1 H), 9.40-9.71 (m, 2 H), 8.56-8.76 (m, 1 H), 7.91 (d, $J = 8.4$ Hz, 1 H), 7.66 (t, $J = 7.6$ Hz, 1 H), 7.13-7.47 (m, 5 H), 4.17-4.39 (m, 1 H), 3.51 (s, 6 H), 2.83-3.16 (m, 4 H), 2.67-2.82 (m, 2 H), 1.38-2.53 (m, 11 H).

Example 77



***cis*- N^2 -[4-(4-Amino-2-trifluoromethoxy-benzylamino)-cyclohexyl]- N^4,N^4 -dimethyl-quinazoline-2,4-diamine trihydrochloride**

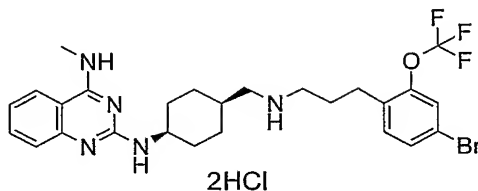
Step A: Synthesis of *cis*- N^2 -[4-(4-amino-2-trifluoromethoxy-benzylamino)-cyclohexyl]- N^4,N^4 -dimethyl-quinazoline-2,4-diamine trihydrochloride.

To a solution of *cis*- N^2 -[4-(4-bromo-2-trifluoromethoxy-benzylamino)-cyclohexyl]- N^4,N^4 -dimethyl-quinazoline-2,4-diamine obtained in step A of example 28 (1.5 g, 2.79 mmol) in EtOH (25 mL) were added copper powder (443 mg, 6.93 mmol), CuCl (690 mg, 2.79 mmol), and 28% aqueous NH_3 (25 mL). The reaction mixture was stirred at reflux for 3.5 hr. The mixture was poured into water, and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated, and purified by medium-pressure liquid chromatography (NH-silica gel, 50% EtOAc in hexane) to give a colorless oil. To a solution of above oil in EtOAc (4 mL) was added 4 M hydrogen chloride in EtOAc (0.25 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated. A solution of the residue in Et_2O (15 mL) was stirred at ambient temperature for 1 hr. The precipitate was collected by filtration, washed with Et_2O , and dried under reduced pressure to give *cis*- N^2 -[4-(4-amino-2-trifluoromethoxy-benzylamino)-cyclohexyl]- N^4,N^4 -dimethyl-quinazoline-2,4-diamine trihydrochloride (104 mg, 6%) as a white solid.

ESI MS m/e 475, M (free) + H^+ ; 1H NMR (300 MHz, $DMSO-d_6$) δ 13.08 (brs, 1 H), 9.15 (brs, 2 H), 8.32-8.48 (m, 1 H), 8.19 (d, $J = 8.1$ Hz, 1 H), 7.73-7.85 (m, 1 H), 7.46 (d, $J =$

8.4 Hz, 1 H), 7.37 (t, $J = 7.4$ Hz, 2 H), 6.56-6.71 (m, 2 H), 3.94-4.26 (m, 3 H), 3.49 (s, 6 H), 3.02-3.24 (m, 1 H), 1.59-2.09 (m, 8 H).

Example 78



***cis*-N²-(4-{[3-(4-Bromo-2-trifluoromethoxy-phenyl)-propylamino]-methyl}-cyclohexyl)-N⁴-methyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of N²-(4-aminomethyl-cyclohexyl)-N⁴-methyl-quinazoline-2,4-diamine

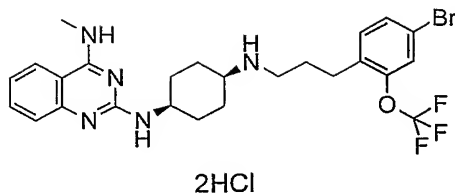
Using the procedure for the step A of example 64, the title compound was obtained. ESI MS m/e 286, $M + H^+$; ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.59 (m, 3 H), 6.97-7.11 (m, 1 H), 5.59 (brs, 1 H), 5.00-5.18 (m, 1 H), 4.21-4.39 (m, 1 H), 3.13 (d, $J = 4.8$ Hz, 3 H), 2.61 (d, $J = 6.2$ Hz, 2 H), 1.57-1.99 (m, 5 H), 1.04-1.52 (m, 4 H).

Step B: Synthesis of *cis*-N²-(4-{[3-(4-bromo-2-trifluoromethoxy-phenyl)-propylamino]-methyl}-cyclohexyl)-N⁴-methyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step D of example 63, the title compound was obtained.

ESI MS m/e 566, M (free) + H^+ ; ¹H NMR (300 MHz, CDCl₃) δ 11.63 (s, 1 H), 9.45 (brs, 3 H), 8.41 (d, $J = 8.5$ Hz, 1 H), 8.32 (d, $J = 7.9$ Hz, 1 H), 7.46 (t, $J = 7.54$ Hz, 1 H), 7.24-7.39 (m, 3 H), 6.99-7.17 (m, 2 H), 4.13-4.35 (m, 1 H), 2.85-3.12 (m, 7 H), 2.75 (t, $J = 7.6$ Hz, 2 H), 2.27-2.47 (m, 2 H), 1.97-2.18 (m, 1 H), 1.37-1.91 (m, 8 H).

Example 79

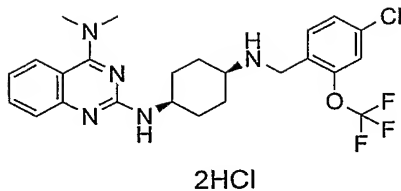


***cis*-N²-{4-[3-(4-Bromo-2-trifluoromethoxy-phenyl)-propylamino]-cyclohexyl}-N⁴-methyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-N²-{4-[3-(4-bromo-2-trifluoromethoxy-phenyl)-propylamino]-cyclohexyl}-N⁴-methyl-quinazoline-2,4-diamine dihydrochloride

To a suspension of *cis*-[4-(4-methylamino-quinazolin-2-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester obtained in step B of example 50 (8.68 g, 23.4 mmol) in CHCl₃ (87mL) was added 4 M hydrogen chloride in EtOAc (100 mL). The reaction mixture was stirred at ambient temperature for 2 hr, and concentrated. The residue was alkalized with saturated aqueous NaHCO₃ and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated (10.57 g). To a suspension of the above residue (594 mg) in MeOH (6 mL) were added 3-(4-bromo-2-trifluoromethoxy-phenyl)-propionaldehyde obtained in step C of example 62 (650 mg, 2.19 mmol), AcOH (132 mg, 2.19 mmol), and NaBH₃CN (207 mg, 3.29 mmol). The reaction mixture was stirred at ambient temperature for 16 hr, poured into saturated aqueous NaHCO₃, and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, purified by medium-pressure liquid chromatography (NH-silica gel, 50% EtOAc in hexane and silica gel, 16% MeOH in CHCl₃) to give a yellow oil. To a solution of the residue in EtOAc (6 mL) was added 4 M hydrogen chloride in EtOAc (0.14 mL). The reaction mixture was stirred at ambient temperature for 30 min, and concentrated. A solution of the residue in Et₂O (10 mL) was stirred at ambient temperature for 1 hr and the precipitate was collected by filtration to give *cis*-N²-{4-[3-(4-bromo-2-trifluoromethoxy-phenyl)-propylamino]-cyclohexyl}-N⁴-methyl-quinazoline-2,4-diamine dihydrochloride (59 mg, 7%) as a white solid.

ESI MS *m/e* 552, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.37 (s, 1 H), 9.78 (brs, 1 H), 9.59 (brs, 2 H), 8.68 (d, *J* = 8.2 Hz, 1 H), 7.55-7.67 (m, 2 H), 7.27-7.43 (m, 5 H), 3.78-3.96 (m, 1 H), 2.94-3.24 (m, 3 H), 2.50-2.89 (m, 5 H), 2.09-2.50 (m, 6 H), 1.60-1.98 (m, 4 H).

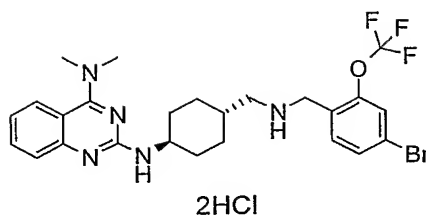
Example 80

***cis*-N²-[4-(4-Chloro-2-trifluoromethoxy-benzylamino)-cyclohexyl]-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-N²-[4-(4-chloro-2-trifluoromethoxy-benzylamino)-cyclohexyl]-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

A mixture of conc. HCl (420 μ L) and NaNO₂ (44 mg, 0.64 mmol) were stirred at 70 °C for 10 min. To the reaction mixture was added a solution of *cis*-N²-[4-(4-amino-2-trifluoromethoxy-benzylamino)-cyclohexyl]-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine (free) obtained in step A of example 77 in AcOH (15 mL), and stirred at ambient temperature for 10 min. To the reaction mixture was added a solution of CuCl (146 mg, 1.47 mmol) in conc. HCl (1 mL), and stirred at 80 °C for 6 hr. The reaction mixture was alkalized with saturated aqueous NaHCO₃, and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, purified by medium-pressure liquid chromatography (NH-silica gel, 50% EtOAc in hexane) to give a yellow oil. To a solution of above oil in EtOAc (2 mL) was added 4 M hydrogen chloride in EtOAc (10 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated. A solution of the residue in Et₂O (20 mL) was stirred at ambient temperature for 1 hr. The precipitate was collected by filtration, washed with Et₂O, and dried under reduced pressure to give *cis*-N²-[4-(4-chloro-2-trifluoromethoxy-benzylamino)-cyclohexyl]-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride (70 mg, 29%) as a white solid.

ESI MS *m/e* 494, M (free) + H⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 12.66 (s, 1 H), 9.82-10.28 (m, 2 H), 8.78 (d, *J* = 7.6 Hz, 1 H), 8.24 (d, *J* = 8.3 Hz, 1 H), 7.92 (d, *J* = 8.2 Hz, 1 H), 7.67 (t, *J* = 7.6 Hz, 1 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 7.18-7.41 (m, 3 H), 4.20-4.44 (m, 3 H), 3.52 (s, 6 H), 3.23 (brs, 1 H), 2.02-2.65 (m, 6 H), 1.75 (t, *J* = 12.8 Hz, 2 H).

Example 81

***trans*-N²-{4-[(4-Bromo-2-trifluoromethoxy-benzylamino)-methyl]-cyclohexyl}-N',N'-dimethyl-quinazoline-2,4-diamine dihydrochloride**

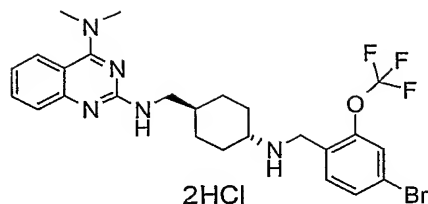
Step A: Synthesis of N²-(4-aminomethyl-cyclohexyl)-N',N'-dimethyl-quinazoline-2,4-diamine

To a suspension of *trans*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester obtained in step B of example 6 (400 mg, 1.00 mmol) in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (5 mL). The mixture was stirred at ambient temperature for 80 min. The reaction mixture was alkalinized with 2 M aqueous sodium hydroxide, and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, purified by medium-pressure liquid chromatography (NH-silica gel, 33% EtOAc in hexane to 3% MeOH in CHCl₃) to give N²-(4-aminomethyl-cyclohexyl)-N',N'-dimethyl-quinazoline-2,4-diamine (250 mg, 83%) as a pale yellow oil.

ESI MS *m/e* 300, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, *J* = 9.3 Hz, 1 H), 7.38-7.53 (m, 2 H), 6.97-7.05 (m, 1 H), 4.77 (d, *J* = 9.3 Hz, 1 H), 3.73-4.02 (m, 1 H), 3.26 (s, 6 H), 2.57 (d, *J* = 6.2 Hz, 2 H), 2.13-2.31 (m, 2 H), 1.75-1.96 (m, 2 H), 0.92-1.45 (m, 7 H).

Step B: Synthesis of *trans*-N²-{4-[(4-bromo-2-trifluoromethoxy-benzylamino)-methyl]-cyclohexyl}-N',N'-dimethyl-quinazoline-2,4-diamine dihydrochloride

Using the procedure for the step B of example 37, the title compound was obtained. ESI MS *m/e* 552, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.72 (s, 1 H), 10.19 (brs, 2 H), 8.18 (d, *J* = 8.9 Hz, 1 H), 8.06 (d, *J* = 7.9 Hz, 1 H), 7.91 (d, *J* = 8.3 Hz, 1 H), 7.42-7.65 (m, 3 H), 7.35 (d, *J* = 8.3 Hz, 1 H), 7.23 (t, *J* = 7.5 Hz, 1 H), 4.18-4.29 (m, 2 H), 3.69-3.89 (m, 1 H), 3.52 (s, 6 H), 2.64-2.81 (m, 2 H), 1.90-2.24 (m, 5 H), 1.02-1.56 (m, 4 H).

Example 82

***trans*-*N*²-[4-(4-Bromo-2-trifluoromethoxy-benzylamino)-cyclohexylmethyl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *trans*-*N*²-(4-amino-cyclohexylmethyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine.

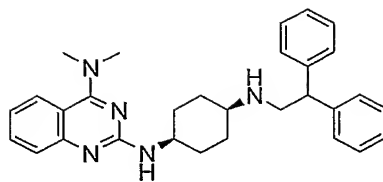
To a solution of *trans*-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexyl}-carbamic acid benzyl ester obtained in step C of example 3 (330 mg, 0.76 mmol) in MeOH (3.3 mL) was added 10% Pd/C (33 mg). The mixture was stirred at ambient temperature under hydrogen atmosphere for 25 hr, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 50% EtOAc in hexane) to give *trans*-*N*²-(4-amino-cyclohexylmethyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine (250 mg, 98%) as a pale yellow oil.

ESI MS *m/e* 300, *M* + *H*⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, *J* = 8.1 Hz, 1 H), 7.40-7.55 (m, 2 H), 6.95-7.07 (m, 1 H), 4.86-5.02 (m, 1 H), 3.36 (t, *J* = 6.3 Hz, 2 H), 3.26 (s, 6 H), 2.53-2.70 (m, 1 H), 1.77-1.98 (m, 4 H), 0.93-1.64 (m, 7 H).

Step B: Synthesis of *trans*-*N*²-[4-(4-bromo-2-trifluoromethoxy-benzylamino)-cyclohexylmethyl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS *m/e* 552, *M* (free)⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.21 (s, 1 H), 10.03 (brs, 2 H), 8.34-8.47 (m, 1 H), 8.07 (d, *J* = 8.4 Hz, 1 H), 7.91 (d, *J* = 8.4 Hz, 1 H), 7.38-7.71 (m, 4 H), 7.20-7.34 (m, 1 H), 4.03-4.20 (m, 2 H), 3.51 (s, 6 H), 3.28-3.42 (m, 2 H), 2.65-2.92 (m, 1 H), 2.16-2.35 (m, 2 H), 1.86-2.05 (m, 2 H), 1.56-1.83 (m, 3 H), 0.89-1.16 (m, 2 H).

Example 83

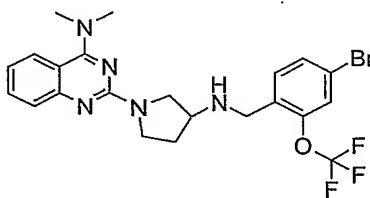
2HCl

***cis*-N²-[4-(2,2-Diphenyl-ethylamino)-cyclohexyl]-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-N²-[4-(2,2-diphenyl-ethylamino)-cyclohexyl]-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS *m/e* 466, M (free) + H⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 12.60 (brs, 1 H), 8.76-9.28 (m, 3 H), 7.91 (d, *J* = 8.3 Hz, 1 H), 7.59-7.71 (m, 2 H), 7.14-7.51 (m, 10 H), 5.00 (t, *J* = 7.7 Hz, 1 H), 4.30-4.40 (m, 1 H), 3.72 (d, *J* = 7.4 Hz, 2 H), 3.51 (s, 6 H), 3.19-3.43 (m, 1 H), 1.85-2.31 (m, 6 H), 1.52-1.76 (s, 2 H).

Example 84

2HCl

{2-[3-(4-Bromo-2-trifluoromethoxy-benzylamino)-pyrrolidin-1-yl]-quinazolin-4-yl}-dimethyl-amine dihydrochloride

Step A: Synthesis of [2-(3-amino-pyrrolidin-1-yl)-quinazolin-4-yl]-dimethyl-amine.

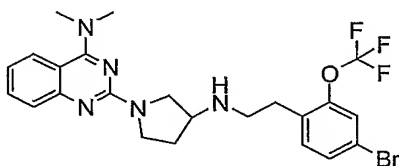
Using the procedure for the step A of example 81, the title compound was obtained.

ESI MS *m/e* 258, M + H⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, *J* = 8.2 Hz, 1 H), 7.41-7.57 (m, 2 H), 6.93-7.06 (m, 1 H), 3.61-4.02 (m, 4 H), 3.40 (dd, *J* = 11.0, 4.97 Hz, 1 H), 3.26 (s, 6 H), 2.09-2.30 (m, 1 H), 1.68-1.87 (m, 1 H), 1.22-1.63 (m, 2 H).

Step B: Synthesis of {2-[3-(4-bromo-2-trifluoromethoxy-benzylamino)-pyrrolidin-1-yl]-quinazolin-4-yl}-dimethyl-amine dihydrochloride

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS m/e 510, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 8.05-8.61 (m, 2 H), 7.61-7.96 (m, 2 H), 7.33-7.57 (m, 2 H), 7.17-7.31 (m, 1 H), 4.42-4.64 (m, 2 H), 4.34 (s, 2 H), 3.58-4.24 (m, 3 H), 3.46 (s, 6 H), 2.81 (brs, 1 H), 2.31-2.60 (m, 1 H).

Example 85

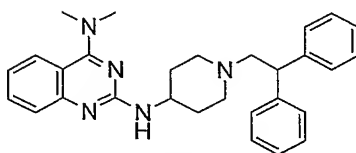
2HCl

(2-{3-[2-(4-Bromo-2-trifluoromethoxy-phenyl)-ethylamino]-pyrrolidin-1-yl}-quinazolin-4-yl)-dimethyl-amine dihydrochloride

Step A: Synthesis of (2-{3-[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethylamino]-pyrrolidin-1-yl}-quinazolin-4-yl)-dimethyl-amine dihydrochloride

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS m/e 524, M (free) H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 8.15-8.53 (m, 1 H), 7.70-7.93 (m, 1 H), 7.62 (t, $J = 7.6$ Hz, 1 H), 7.11-7.46 (m, 4 H), 3.60-4.70 (m, 5 H), 3.45 (s, 6 H), 3.04-3.59 (m, 4 H), 2.29-2.98 (m, 2 H).

Example 86

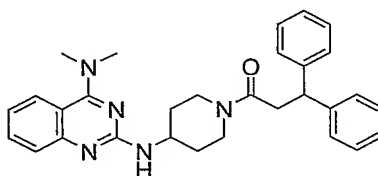
2HCl

***N*²-[1-(2,2-Diphenyl-ethyl)-piperidin-4-yl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *N*²-[1-(2,2-diphenyl-ethyl)-piperidin-4-yl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride

Using the procedure for the step B of example 37, the title compound was obtained. ESI MS *m/e* 452, *M* (free) + *H*⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 12.54 (brs, 1 H), 12.42 (s, 1 H), 9.82 (d, *J* = 8.4 Hz, 1 H), 7.92 (d, *J* = 8.1 Hz, 1 H), 7.66-7.74 (m, 1 H), 7.40-7.54 (m, 5 H), 7.27-7.39 (m, 5 H), 7.14-7.26 (m, 2 H), 5.17 (t, *J* = 6.3 Hz, 1 H), 4.39-4.56 (m, 1 H), 3.70-3.87 (m, 2 H), 3.34-3.60 (m, 7 H), 3.07-3.25 (m, 2 H), 2.55-2.87 (m, 2 H), 1.61-1.94 (m, 4 H).

Example 87



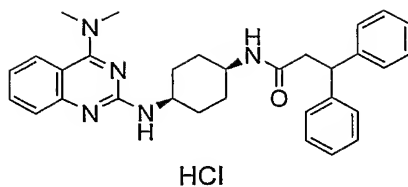
HCl

1-[4-(4-Dimethylamino-quinazolin-2-ylamino)-piperidin-1-yl]-3,3-diphenyl-propan-1-one hydrochloride

Step A: Synthesis of 1-[4-(4-dimethylamino-quinazolin-2-ylamino)-piperidin-1-yl]-3,3-diphenyl-propan-1-one hydrochloride

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 502, *M* + Na⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 13.45 (brs, 1 H), 8.73 (d, *J* = 6.9 Hz, 1 H), 7.89 (d, *J* = 8.2 Hz, 1 H), 7.61-7.70 (m, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.25-7.39 (m, 11 H), 4.67 (t, *J* = 7.5 Hz, 1 H), 3.97-4.14 (m, 2 H), 3.70-3.89 (m, 1 H), 3.50 (s, 6 H), 3.13-3.30 (m, 2 H), 2.99-3.12 (m, 2 H), 1.31-1.99 (m, 4 H).

Example 88

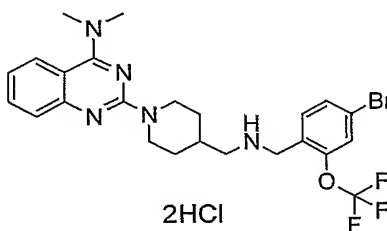


***cis*-N-[4-(4-Dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-3,3-diphenyl-propionamide hydrochloride**

Step A: Synthesis of *cis*-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-3,3-diphenyl-propionamide hydrochloride

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS m/e 494, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 13.20 (s, 1 H), 8.77 (d, J = 8.2 Hz, 1 H), 7.88 (d, J = 7.7 Hz, 1 H), 7.60-7.69 (m, 1 H), 7.53 (d, J = 17.1 Hz, 1 H), 7.12-7.33 (m, 11 H), 5.72 (d, J = 9.2 Hz, 1 H), 4.57 (t, J = 8.0 Hz, 1 H), 4.11-4.23 (m, 1 H), 3.72-3.87 (m, 1 H), 3.49 (s, 6 H), 2.88 (d, J = 7.9 Hz, 2 H), 1.47-1.85 (m, 8 H).

Example 89



(2-{4-[(4-Bromo-2-trifluoromethoxy-benzylamino)-methyl]-piperidin-1-yl}-quinazolin-4-yl)-dimethyl-amine dihydrochloride

Step A: Synthesis of [2-(4-aminomethyl-piperidin-1-yl)-quinazolin-4-yl]-dimethyl-amine.

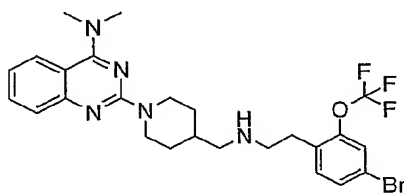
Using the procedure for the step A of example 64, the title compound was obtained. ESI MS m/e 286, M + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 1 H), 7.42-7.52 (m, 1 H), 7.23-7.36 (m, 1 H), 6.94-7.07 (m, 1 H), 4.94 (d, J = 12.7 Hz, 2 H), 3.26 (s, 6 H), 2.74-3.01 (m, 2 H), 2.61 (d, J = 6.6 Hz, 2 H), 1.46-1.99 (m, 4 H), 1.01-1.39 (m, 3 H).

Step B: Synthesis of (2-{4-[(4-bromo-2-trifluoromethoxy-benzylamino)-methyl]-piperidin-1-yl}-quinazolin-4-yl)-dimethyl-amine dihydrochloride.

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS m/e 538, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 12.66 (s, 1 H), 8.50 (d, J = 8.1 Hz, 1 H), 8.23 (d, J = 8.6 Hz, 1 H), 7.88 (d, J = 8.4 Hz, 1 H), 7.66 (t, J = 7.9 Hz, 1 H), 7.50 (dd, J = 8.4, 1.9 Hz, 1 H), 7.36-7.41 (m, 1 H), 7.24-7.34 (m, 1 H), 5.01 (brs, 2 H), 4.27 (s, 2 H), 3.49 (s, 6 H), 3.05-3.37 (m, 2 H), 2.44-2.92 (m, 3 H), 1.82-2.37 (m, 2 H), 1.14-1.62 (m, 2 H).

Example 90



2HCl

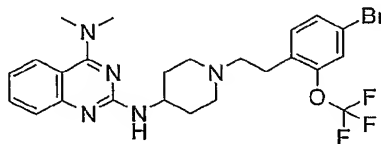
[2-(4-{[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethylamino]-methyl}-piperidin-1-yl)-quinazolin-4-yl]-dimethyl-amine dihydrochloride

Step A: Synthesis of [2-(4-{[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethylamino]-methyl}-piperidin-1-yl)-quinazolin-4-yl]-dimethyl-amine dihydrochloride.

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS m/e 552, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 12.63 (s, 1 H), 8.48 (d, J = 8.2 Hz, 1 H), 7.79-7.97 (d, J = 7.5 Hz, 1 H), 7.58-7.73 (m, 1 H), 7.19-7.48 (m, 4 H), 5.02 (brs, 2 H), 3.49 (s, 6 H), 2.82-3.69 (m, 6 H), 1.98-2.79 (m, 5 H), 1.52 (brs, 2 H).

Example 91



2HCl

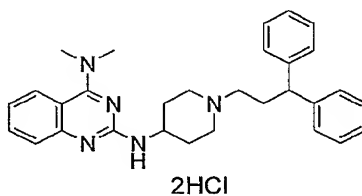
***N*²-{1-[2-(4-Bromo-2-trifluoromethoxy-phenyl)-ethyl]-piperidin-4-yl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *N*²-{1-[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethyl]-piperidin-4-yl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS *m/e* 538, M (free) + H⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 12.61 (brs, 1 H), 12.43 (s, 1 H), 9.97 (d, *J* = 8.1 Hz, 1 H), 7.94 (d, *J* = 7.9 Hz, 1 H), 7.65-7.76 (m, 1 H), 7.28-7.52 (m, 5 H), 4.48-4.62 (m, 1 H), 3.12-3.73 (m, 14 H), 2.68-2.92 (m, 2 H), 1.96-2.13 (m, 2 H).

Example 92

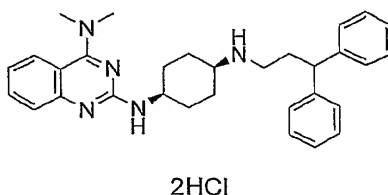


***N*²-[1-(3,3-Diphenyl-propyl)-piperidin-4-yl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *N*²-[1-(3,3-diphenyl-propyl)-piperidin-4-yl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of example 72, the title compound was obtained. ESI MS *m/e* 466, M (free) + H⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 12.42 (s, 1 H), 12.26 (brs, 1 H), 9.87 (d, *J* = 8.2 Hz, 1 H), 7.93 (d, *J* = 8.2 Hz, 1 H), 7.65-7.74 (m, 1 H), 7.47 (d, *J* = 8.2 Hz, 1 H), 7.13-7.37 (m, 11 H), 4.44-4.60 (m, 1 H), 3.98 (t, *J* = 7.9 Hz, 1 H), 3.28-3.65 (m, 10 H), 2.93-3.09 (m, 2 H), 2.63-2.88 (m, 4 H), 1.84-2.02 (m, 2 H).

Example 93

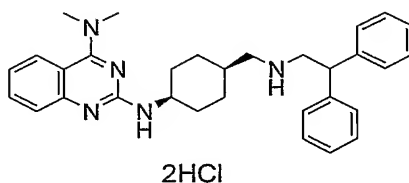


***cis*-*N*²-[4-(3,3-Diphenyl-propylamino)-cyclohexyl]-*N*^t,*N*^t-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-*N*²-[4-(3,3-diphenyl-propylamino)-cyclohexyl]-*N*^t,*N*^t-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of example 72, the title compound was obtained. ESI MS *m/e* 480, M (free) + H⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 12.58 (s, 1 H), 9.53 (s, 2 H), 8.58 (d, *J* = 7.9 Hz, 1 H), 7.91 (d, *J* = 8.1 Hz, 1 H), 7.64 (t, *J* = 7.7 Hz, 1 H), 7.48 (d, *J* = 7.9 Hz, 1 H), 7.08-7.33 (m, 11 H), 4.18-4.33 (m, 1 H), 4.11 (t, *J* = 7.7 Hz, 1 H), 3.50 (s, 6 H), 3.16 (brs, 1 H), 2.96 (brs, 2 H), 2.64-2.84 (m, 2 H), 1.87-2.25 (m, 6 H), 1.53-1.75 (m, 2 H).

Example 94



***cis*-*N*²-{4-[(2,2-Diphenyl-ethylamino)-methyl]-cyclohexyl}-*N*^t,*N*^t-dimethyl-quinazoline-2,4-diamine dihydrochloride**

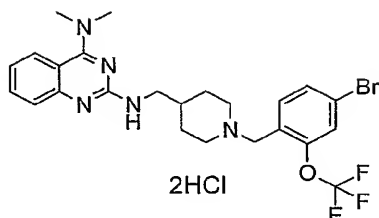
Step A: Synthesis of *cis*-*N*²-{4-[(2,2-diphenyl-ethylamino)-methyl]-cyclohexyl}-*N*^t,*N*^t-dimethyl-quinazoline-2,4-diamine dihydrochloride

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS *m/e* 480, M (free) + H⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 12.78 (s, 1 H), 8.94 (brs, 2 H), 8.80 (d, *J* = 8.4 Hz, 1 H), 7.89 (d, *J* = 8.1 Hz, 1 H), 7.60-7.69 (m, 1 H), 7.44-7.58 (m, 2 H), 7.18-7.42 (m, 9 H), 4.91 (t, *J* = 8.0 Hz, 1 H), 4.19-4.34 (m, 1 H), 3.61-3.76 (m, 2 H),

3.50 (s, 6 H), 2.81-2.97 (m, 2 H), 2.04-2.19 (m, 1 H), 1.74-1.91 (m, 2 H), 1.45-1.69 (m, 6 H).

Example 95



***N*²-[1-(4-Bromo-2-trifluoromethoxy-benzyl)-piperidin-4-ylmethyl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *N*⁴,*N*⁴-dimethyl-*N*²-piperidin-4-ylmethyl-quinazoline-2,4-diamine.

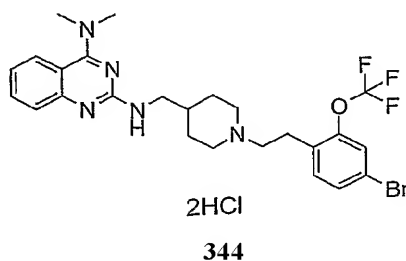
Using the procedure for the step A of example 81, the title compound was obtained. ESI MS *m/e* 408, M + Na⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.82 (d, *J* = 8.3 Hz, 1 H), 7.39-7.59 (m, 2 H), 6.96-7.12 (m, 1 H), 4.79-5.11 (m, 1 H), 3.94-4.31 (m, 2 H), 3.42 (t, *J* = 5.9 Hz, 2 H), 3.27 (s, 6 H), 2.70 (t, *J* = 12.1 Hz, 2 H), 1.63-1.92 (m, 3 H), 1.46 (s, 9 H), 0.99-1.37 (m, 2 H).

Step B: Synthesis of *N*²-[1-(4-bromo-2-trifluoromethoxy-benzyl)-piperidin-4-ylmethyl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS *m/e* 538, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.13 (s, 1 H), 12.69 (brs, 1 H), 8.73 (t, *J* = 6.3 Hz, 1 H), 8.19 (d, *J* = 8.2 Hz, 1 H), 7.90 (d, *J* = 7.6 Hz, 1 H), 7.45-7.73 (m, 4 H), 7.22-7.33 (m, 1 H), 4.10-4.24 (m, 2 H), 3.36-3.67 (m, 10 H), 2.61-2.86 (m, 2 H), 1.80-2.33 (m, 5 H).

Example 96



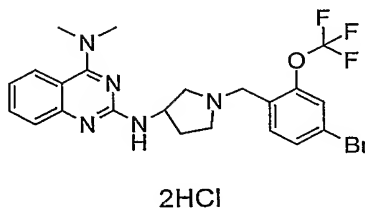
***N*²-{1-[2-(4-Bromo-2-trifluoromethoxy-phenyl)-ethyl]-piperidin-4-ylmethyl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *N*²-{1-[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethyl]-piperidin-4-ylmethyl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS *m/e* 552, M (free) + H⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 13.16 (brs, 1 H), 8.74 (m, 1 H), 7.92 (d, *J* = 8.2 Hz, 1 H), 7.67 (t, *J* = 7.5 Hz, 1 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.22-7.46 (m, 5 H), 3.44-3.71 (m, 10 H), 3.26-3.39 (m, 2 H), 3.01-3.15 (m, 2 H), 2.63-2.86 (m, 2 H), 1.87-2.33 (m, 5 H).

Example 97



***N*²-[1-(4-Bromo-2-trifluoromethoxy-benzyl)-pyrrolidin-3-yl]-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *N*²-(1-benzyl-pyrrolidin-3-yl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine.

A mixture of (2-chloro-quinazolin-4-yl)-dimethyl-amine obtained in step B of example 1 (5.1 g, 28.9 mmol) and 1-Benzyl-pyrrolidin-3-ylamine (5.1 g, 28.9 mmol) in BuOH (8 mL) was stirred at reflux for 26 hr, poured into saturated aqueous NaHCO₃, and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, 10% to 16% EtOAc in hexane) to give *N*²-(1-benzyl-pyrrolidin-3-yl)-*N*⁴,*N*⁴-dimethyl-

quinazoline-2,4-diamine (3.37 g, 50%) as a pale yellow solid.

ESI MS m/e 348, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, $J = 9.0$ Hz, 1 H), 7.46 (m, 2 H), 7.18-7.38 (m, 5 H), 7.02 (ddd, $J = 8.3, 6.3, 1.9$ Hz, 1 H), 5.30 (brs, 1 H), 4.59-4.75 (m, 1 H), 3.63 (d, $J = 2.5$ Hz, 2 H), 3.25 (s, 6 H), 2.88 (dd, $J = 9.6, 6.6$ Hz, 1 H), 2.70-2.81 (m, 1 H), 2.28-2.60 (m, 3 H), 1.64-1.78 (m, 1 H).

Step B: Synthesis of N^4, N^4 -dimethyl- N^2 -pyrrolidin-3-yl-quinazoline-2,4-diamine.

To a solution of N^2 -(1-benzyl-pyrrolidin-3-yl)- N^4, N^4 -dimethyl-quinazoline-2,4-diamine (3.3 g, 9.5 mmol) in MeOH (33 mL) was added $Pd(OH)_2$ (660 mg). The mixture was stirred at ambient temperature under hydrogen atmosphere for 13 hr, and stirred at 50 °C for 6 hr. The mixture was filtered, concentrated, and purified by medium-pressure liquid chromatography (NH-silica gel, 1% to 3% MeOH in $CHCl_3$) to give N^4, N^4 -dimethyl- N^2 -pyrrolidin-3-yl-quinazoline-2,4-diamine (2.3 g, 93%) as a yellow oil.

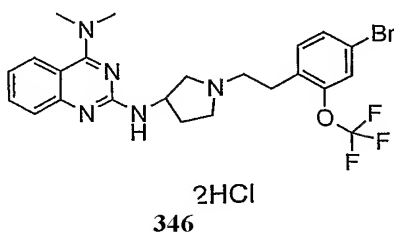
ESI MS m/e 258, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, $J = 7.8$ Hz, 1 H), 7.42-7.54 (m, 2 H), 7.03 (ddd, $J = 8.3, 6.4, 1.8$ Hz, 1 H), 5.03 (brs, 1 H), 4.52 (brs, 1 H), 3.26 (s, 6 H), 2.83-3.24 (m, 4 H), 1.97-2.30 (m, 2 H), 1.57-1.77 (m, 1 H).

Step C: Synthesis of N^2 -[1-(4-bromo-2-trifluoromethoxy-benzyl)-pyrrolidin-3-yl]- N^4, N^4 -dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS m/e 510, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 13.22 (brs, 1 H), 12.87 (s, 1 H), 9.68 (d, $J = 7.4$ Hz, 1 H), 8.11 (d, $J = 8.4$ Hz, 1 H), 7.95 (d, $J = 8.4$ Hz, 1 H), 7.71 (t, $J = 8.3$ Hz, 1 H), 7.43-7.63 (m, 3 H), 7.28-7.38 (m, 1 H), 4.94-5.15 (m, 1 H), 4.41 (s, 2 H), 4.00-4.17 (m, 1 H), 3.26-3.82 (m, 8 H), 3.00-3.16 (m, 1 H), 2.59-2.82 (m, 1 H), 2.18-2.37 (m, 1 H).

Example 98



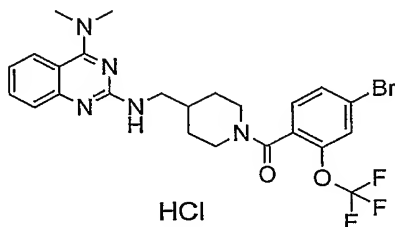
***N*²-{1-[2-(4-Bromo-2-trifluoromethoxy-phenyl)-ethyl]-pyrrolidin-3-yl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *N*²-{1-[2-(4-bromo-2-trifluoromethoxy-phenyl)-ethyl]-pyrrolidin-3-yl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step B of example 37, the title compound was obtained.

ESI MS *m/e* 524, M (free) + H⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 9.61-9.78 (m, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.71 (t, *J* = 7.7 Hz, 1 H), 7.55 (d, *J* = 8.2 Hz, 1 H), 7.29-7.47 (m, 4 H), 4.89-5.12 (m, 1 H), 4.07-4.28 (m, 1 H), 2.99-3.97 (m, 13 H), 2.55-2.79 (m, 1 H), 2.22-2.42 (m, 1 H).

Example 99

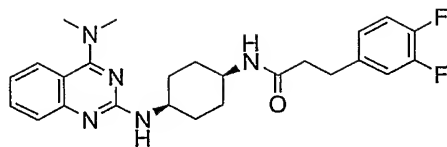


1-(4-Bromo-2-trifluoromethoxy-phenyl)-1-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-piperidin-1-yl}-methanone hydrochloride

Step A: Synthesis of 1-(4-bromo-2-trifluoromethoxy-phenyl)-1-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-piperidin-1-yl}-methanone hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 552, M (free) + H⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 13.44 (brs, 1 H), 8.53-8.77 (m, 1 H), 7.90 (d, *J* = 8.5 Hz, 1 H), 7.66 (t, *J* = 7.7 Hz, 1 H), 7.43-7.61 (m, 3 H), 7.19-7.37 (m, 1 H), 4.69-4.85 (m, 1 H), 3.20-3.63 (m, 10 H), 2.61-3.13 (m, 2 H), 1.76-2.14 (m, 3 H), 1.08-1.48 (m, 2 H).

Example 100



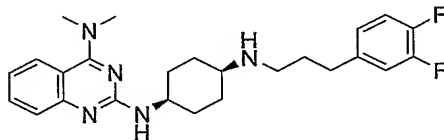
HCl

***cis*-3-(3,4-Difluoro-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-propionamide hydrochloride**

Step A: Synthesis of *cis*-3-(3,4-difluoro-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-propionamide hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 454, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.05 (s, 1 H), 8.87 (d, *J* = 8.1 Hz, 1 H), 7.89 (d, *J* = 8.2 Hz, 1 H), 7.65 (t, *J* = 7.7 Hz, 1 H), 7.51 (d, *J* = 7.3 Hz, 1 H), 7.20-7.27 (m, 1 H), 6.88-7.09 (m, 3 H), 5.97 (d, *J* = 8.5 Hz, 1 H), 4.26 (brs, 1 H), 3.91 (brs, 1 H), 3.51 (s, 6 H), 2.92 (t, *J* = 7.6 Hz, 2 H), 2.44 (t, *J* = 7.6 Hz, 2 H), 1.61-1.93 (brs, 8 H).

Example 101



2HCl

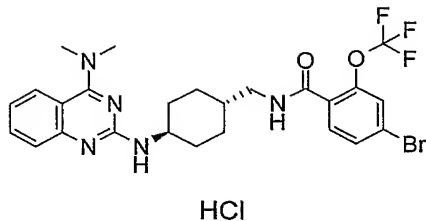
***cis*-*N*²-{4-[3-(3,4-Difluoro-phenyl)-propylamino]-cyclohexyl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-*N*²-{4-[3-(3,4-difluoro-phenyl)-propylamino]-cyclohexyl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of example 72, the title compound was obtained. ESI MS *m/e* 440, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.62 (s, 1 H), 9.54 (s, 2 H), 8.72 (d, *J* = 7.6 Hz, 1 H), 7.91 (d, *J* = 8.4 Hz, 1 H), 7.62-7.70 (m, 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.24-7.33 (m, 1 H), 6.90-7.06 (m, 3 H), 4.29 (brs, 1 H), 3.52 (s, 6 H), 3.00-3.42

(m, 3 H), 2.67-2.81 (m, 2 H), 1.93-2.43 (m, 8 H), 1.60-1.80 (m, 2 H).

Example 102



***trans*-4-Bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamide hydrochloride**

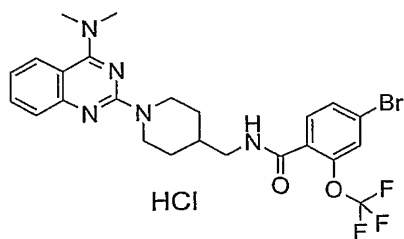
Step A: Synthesis of *N*²-(4-aminomethyl-cyclohexyl)-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine.

Using the procedure for the step A of example 81, the title compound was obtained. ESI MS *m/e* 300, *M* + *H*⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.79 (d, *J* = 8.4 Hz, 1 H), 7.45 (m, 2 H), 7.00 (ddd, *J* = 8.4, 6.3, 1.9 Hz, 1 H), 4.80 (d, *J* = 8.2 Hz, 1 H), 3.82-3.94 (m, 1 H), 3.24 (s, 6 H), 2.56 (d, *J* = 6.2 Hz, 2 H), 2.14-2.28 (m, 2 H), 1.78-1.92 (m, 2 H), 0.95-1.42 (m, 7 H).

Step B: Synthesis of *trans*-4-bromo-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-2-trifluoromethoxy-benzamide hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 566, *M* + *H*⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.48 (s, 1 H), 8.34 (d, *J* = 7.5 Hz, 1 H), 7.83-7.94 (m, 2 H), 7.43-7.69 (m, 4 H), 7.20-7.29 (m, 1 H), 6.49-6.62 (m, 1 H), 3.72-3.93 (m, 1 H), 3.50 (s, 6 H), 3.39 (t, *J* = 6.3 Hz, 2 H), 2.09-2.22 (m, 2 H), 1.85-1.98 (m, 2 H), 1.37-1.69 (m, 3 H), 1.08-1.28 (m, 2 H).

Example 103

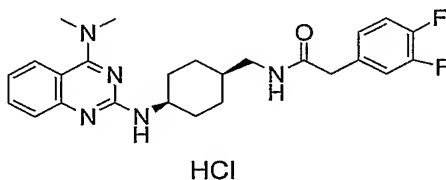


4-Bromo-*N*-[1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-ylmethyl]-2-trifluoromethoxy-benzamide hydrochloride

Step A: Synthesis of 4-bromo-*N*-[1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-ylmethyl]-2-trifluoromethoxy-benzamide hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS m/e 552, M (free)⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.50 (s, 1 H), 8.73 (d, J = 8.5 Hz, 1 H), 7.86 (d, J = 8.4 Hz, 1 H), 7.81 (d, J = 8.4 Hz, 1 H), 7.62-7.71 (m, 1 H), 7.53 (dd, J = 8.4, 1.87 Hz, 1 H), 7.45 (s, 1 H), 7.23-7.32 (m, 1 H), 6.77-6.87 (m, 1 H), 3.30-3.55 (m, 10 H), 2.96-3.27 (m, 2 H), 1.89-2.15 (m, 3 H), 1.28-1.57 (m, 2 H).

Example 104

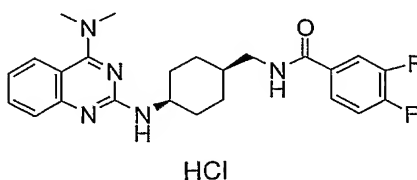


***cis*-2-(3,4-Difluoro-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide hydrochloride**

Step A: Synthesis of *cis*-2-(3,4-difluoro-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide hydrochloride

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS m/e 454, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.66 (s, 1 H), 9.08 (d, J = 8.9 Hz, 1 H), 7.90 (d, J = 8.1 Hz, 1 H), 7.66 (ddd, J = 8.4, 7.2, 1.2 Hz, 1 H), 7.48 (dd, J = 8.4, 0.9 Hz, 1 H), 7.32-7.41 (m, 1 H), 7.12-7.31 (m, 3 H), 6.97-7.08 (m, 1 H), 4.35-4.48 (m, 1 H), 3.78 (s, 2 H), 3.52 (s, 6 H), 3.28-3.36 (m, 2 H), 1.42-2.05 (m, 9 H).

Example 105



***cis*-N-[4-(4-Dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-3,4-difluorobenzamide hydrochloride**

Step A: Synthesis of *cis*-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-3,4-difluorobenzamide hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 440, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.89 (s, 1 H), 9.11 (d, *J* = 8.2 Hz, 1 H), 7.88 (m, 3 H), 7.64 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1 H), 7.49 (dd, *J* = 8.4, 0.9 Hz, 1 H), 7.18-7.29 (m, 2 H), 6.96-7.07 (m, 1 H), 4.29-4.44 (m, 1 H), 3.51 (s, 8 H), 1.55-2.02 (m, 9 H).

Example 106

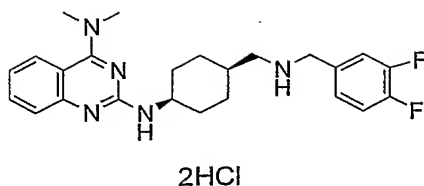


***cis*-N²-(4-([2-(3,4-Difluoro-phenyl)-ethylamino]-methyl)-cyclohexyl)-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-N²-(4-([2-(3,4-difluoro-phenyl)-ethylamino]-methyl)-cyclohexyl)-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of example 72, the title compound was obtained. ESI MS *m/e* 440, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 12.43 (s, 1 H), 9.64 (brs, 2 H), 8.66 (d, *J* = 8.3 Hz, 1 H), 7.91 (d, *J* = 8.3 Hz, 1 H), 7.67 (t, *J* = 7.8 Hz, 1 H), 7.46 (d, *J* = 8.3 Hz, 1 H), 7.28 (t, *J* = 7.8 Hz, 1 H), 6.97-7.17 (m, 3 H), 4.24-4.37 (m, 1 H), 3.52 (s, 6 H), 3.30-3.44 (m, 2 H), 2.94-3.25 (m, 4 H), 1.57-2.28 (m, 9 H).

Example 107

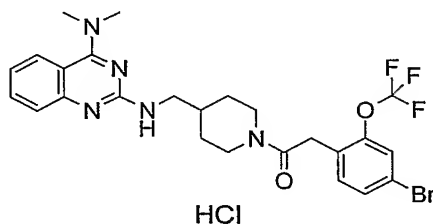


***cis*-N²-{4-[(3,4-Difluoro-benzylamino)-methyl]-cyclohexyl}-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-N²-{4-[(3,4-difluoro-benzylamino)-methyl]-cyclohexyl}-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride

Using the procedure for the step A of example 72, the title compound was obtained. ESI MS m/e 426, M (free) + H⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 9.39 (s, 2 H), 8.44 (m, 1 H), 8.17 (d, *J* = 8.4 Hz, 1 H), 7.72-7.88 (m, 2 H), 7.27-7.61 (m, 4 H), 4.11-4.31 (m, 3 H), 3.48 (s, 6 H), 2.81 (d, *J* = 6.1 Hz, 2 H), 1.32-2.03 (m, 9 H).

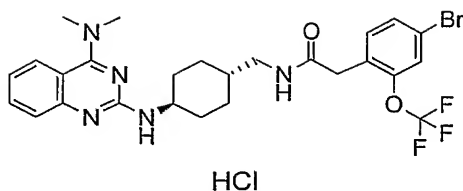
Example 108



2-(4-Bromo-2-trifluoromethoxy-phenyl)-1-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-piperidin-1-yl}-ethanone hydrochloride

Step A: Synthesis of 2-(4-bromo-2-trifluoromethoxy-phenyl)-1-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-piperidin-1-yl}-ethanone hydrochloride.

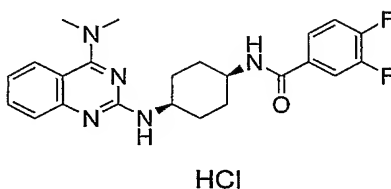
Using the procedure for the step A of example 47, the title compound was obtained. ESI MS m/e 566, M (free) + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.48 (s, 1 H), 8.65 (t, *J* = 5.8 Hz, 1 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 7.53-7.70 (m, 2 H), 7.37-7.44 (m, 2 H), 7.20-7.32 (m, 2 H), 4.59-4.72 (m, 1 H), 3.80-3.94 (m, 1 H), 3.68 (d, *J* = 6.1 Hz, 2 H), 3.25-3.58 (m, 8 H), 2.94-3.12 (m, 1 H), 2.50-2.68 (m, 1 H), 1.75-2.03 (m, 3 H), 1.06-1.32 (m, 2 H).

Example 109

***trans*-2-(4-Bromo-2-trifluoromethoxy-phenyl)-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide**

Step A: Synthesis of *trans*-2-(4-bromo-2-trifluoromethoxy-phenyl)-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 580, M (free)⁺; ¹H NMR (300 MHz, CDCl₃) δ 8.28 (d, *J* = 6.7 Hz, 1 H), 7.87-7.90 (d, *J* = 8.5 Hz, 1 H), 7.52-7.66 (m, 2 H), 7.39-7.44 (m, 2 H), 7.20-7.33 (m, 2 H), 5.85-5.98 (m, 1 H), 3.70-3.91 (m, 1 H), 3.58 (s, 2 H), 3.50 (s, 6 H), 3.16 (t, *J* = 6.5 Hz, 2 H), 2.03-2.20 (m, 2 H), 1.28-1.88 (m, 5 H), 0.96-1.18 (m, 2 H).

Example 110

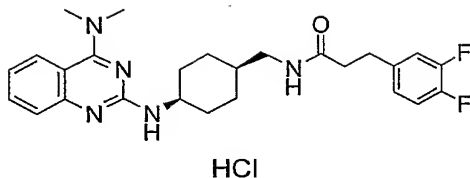
***cis*-N-[4-(4-Dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-3,4-difluorobenzamide hydrochloride**

Step A: Synthesis of *cis*-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-3,4-difluorobenzamide hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 448, M (free) + Na⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.01 (s, 1 H), 8.96 (d, *J* = 8.1 Hz, 1 H), 7.91 (d, *J* = 8.2 Hz, 1 H), 7.55-7.79 (m, 4 H), 7.49-7.54 (m, 1 H), 7.15-7.32 (m, 2 H), 6.76 (d, *J* = 8.4 Hz, 1 H), 4.30-4.41 (m, 1 H), 4.03-4.22 (m, 1 H), 3.52 (s, 6 H),

1.67-2.07 (m, 8 H).

Example 111

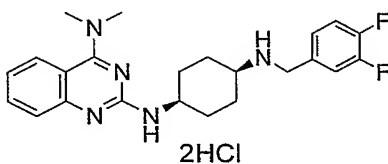


***cis*-3-(3,4-Difluoro-phenyl)-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-propionamide hydrochloride**

Step A: Synthesis of *cis*-3-(3,4-difluoro-phenyl)-N-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-propionamide hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 468, M (free) + H⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 12.70 (s, 1 H), 9.00 (d, *J* = 8.3 Hz, 1 H), 7.90 (d, *J* = 8.3 Hz, 1 H), 7.66 (ddd, *J* = 8.3, 7.2, 1.0 Hz, 1 H), 7.48 (dd, *J* = 8.3, 1.0 Hz, 1 H), 7.11-7.31 (m, 2 H), 6.84-7.06 (m, 3 H), 4.32-4.44 (m, 1 H), 3.51 (s, 6 H), 3.26-3.33 (m, 2 H), 2.96 (t, *J* = 7.5 Hz, 2 H), 2.76 (t, *J* = 7.4 Hz, 2 H), 1.34-1.94 (m, 9 H).

Example 112



***cis*-N²-[4-(3,4-Difluoro-benzylamino)-cyclohexyl]-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

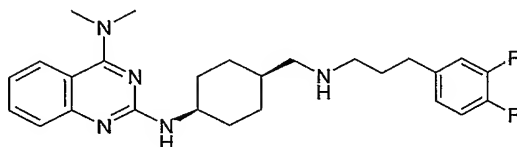
Step A: Synthesis of *cis*-N²-[4-(3,4-difluoro-benzylamino)-cyclohexyl]-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of example 72, the title compound was obtained.

ESI MS *m/e* 434, M (free) + Na⁺ ; ¹H NMR (300 MHz, DMSO-d₆) δ 13.03 (s, 1 H), 9.50

(brs, 2 H), 8.31-8.40 (m, 1 H), 8.19 (d, $J = 8.2$ Hz, 1 H), 7.73-7.90 (m, 2 H), 7.29-7.60 (m, 4 H), 4.04-4.28 (m, 3 H), 3.46 (s, 6 H), 3.06-3.22 (m, 1 H), 1.61-2.10 (m, 8 H).

Example 113



2HCl

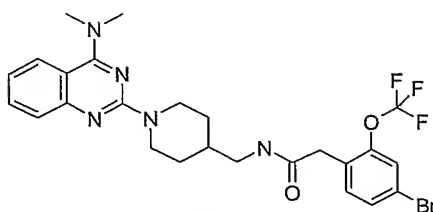
***cis*-N²-(4-([3-(3,4-Difluoro-phenyl)-propylamino]-methyl)-cyclohexyl)-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-N²-(4-([3-(3,4-difluoro-phenyl)-propylamino]-methyl)-cyclohexyl)-N⁴,N⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of example 72, the title compound was obtained.

ESI MS m/e 454, M (free) + H⁺ ; ¹H NMR (300 MHz, CDCl₃) δ 12.50 (s, 1 H), 9.43 (brs, 2 H), 8.60 (d, $J = 7.93$ Hz, 1 H), 7.90 (d, $J = 8.2$ Hz, 1 H), 7.65 (ddd, $J = 8.2, 7.2, 1.1$ Hz, 1 H), 7.46 (d, $J = 8.6$ Hz, 1 H), 7.23-7.30 (m, 1 H), 6.91-7.08 (m, 3 H), 4.22-4.34 (m, 1 H), 3.51 (s, 6 H), 2.87-3.07 (m, 4 H), 2.68 (t, $J = 7.7$ Hz, 2 H), 1.53-2.43 (m, 11 H).

Example 114



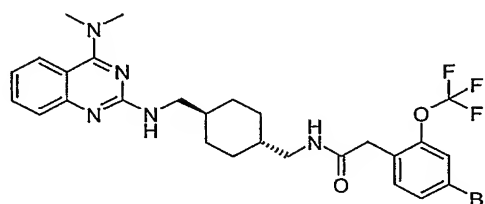
HCl

2-(4-Bromo-2-trifluoromethoxy-phenyl)-N-[1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-ylmethyl]-acetamide hydrochloride

Step A: Synthesis of 2-(4-bromo-2-trifluoromethoxy-phenyl)-N-[1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-ylmethyl]-acetamide hydrochloride

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS m/e 588, M (free) + Na^+ ; ^1H NMR (300 MHz, CDCl_3) δ 13.32 (s, 1 H), 8.68 (d, $J = 8.4$ Hz, 1 H), 7.86 (d, $J = 7.4$ Hz, 1 H), 7.65 (ddd, $J = 8.4, 7.1, 1.2$ Hz, 1 H), 7.23-7.42 (m, 4 H), 6.59-6.69 (m, 1 H), 3.60 (s, 2 H), 3.48 (s, 7 H), 2.90-3.37 (m, 5 H), 1.78-2.08 (m, 3 H), 1.19-1.46 (m, 2 H).

Example 115



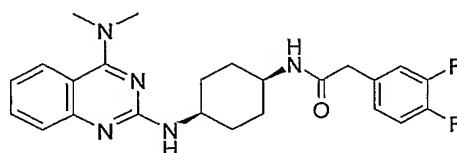
HCl

***trans*-2-(4-Bromo-2-trifluoromethoxy-phenyl)-N-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-acetamide hydrochloride**

StepA: Synthesis of *trans*-2-(4-bromo-2-trifluoromethoxy-phenyl)-N-{4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-acetamide hydrochloride.

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS m/e 616, M (free) + Na^+ ; ^1H NMR (300 MHz, CDCl_3) δ 8.37-8.49 (m, 1 H), 7.89 (d, $J = 8.5$ Hz, 1 H), 7.53-7.68 (m, 2 H), 7.40-7.45 (m, 2 H), 7.20-7.32 (m, 2 H), 5.60-5.71 (m, 1 H), 3.55 (s, 2 H), 3.50 (s, 6 H), 3.35 (t, $J = 6.1$ Hz, 2 H), 3.08 (t, $J = 6.4$ Hz, 2 H), 0.77-2.00 (m, 10 H).

Example 116



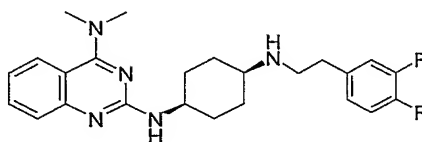
HCl

***cis*-2-(3,4-Difluoro-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-acetamide hydrochloride**

Step A: Synthesis of *cis*-2-(3,4-difluoro-phenyl)-*N*-[4-(4-dimethylamino-quinazolin-2-ylamino)-cyclohexyl]-acetamide hydrochloride

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 440, *M* (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 13.01 (s, 1 H), 8.85 (d, J = 8.2 Hz, 1 H), 7.89 (d, J = 8.2 Hz, 1 H), 7.65 (ddd, J = 8.2, 7.1, 1.2 Hz, 1 H), 7.52 (d, J = 8.2 Hz, 1 H), 6.95-7.33 (m, 4 H), 6.32 (d, J = 7.6 Hz, 1 H), 4.19-4.34 (m, 1 H), 3.82-4.01 (m, 1 H), 3.51 (s, 6 H), 3.47 (s, 2 H), 1.61-2.01 (m, 8 H).

Example 117

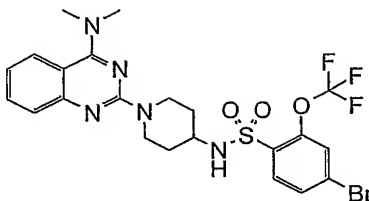


2HCl

***cis*-*N*²-{4-[2-(3,4-Difluoro-phenyl)-ethylamino]-cyclohexyl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride**

Step A: Synthesis of *cis*-*N*²-{4-[2-(3,4-difluoro-phenyl)-ethylamino]-cyclohexyl}-*N*⁴,*N*⁴-dimethyl-quinazoline-2,4-diamine dihydrochloride.

Using the procedure for the step A of example 72, the title compound was obtained. ESI MS *m/e* 426, *M* (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 12.51 (s, 1 H), 9.70 (brs, 2 H), 8.67 (d, J = 7.5 Hz, 1 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.68 (t, J = 8.0 Hz, 1 H), 7.52 (d, J = 8.4 Hz, 1 H), 7.30 (t, J = 7.8 Hz, 1 H), 6.97-7.22 (m, 3 H), 4.34 (brs, 1 H), 3.53 (s, 6 H), 3.12-3.41 (m, 5 H), 1.62-2.40 (m, 8 H).

Example 118**4-Bromo-N-[1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-yl]-2-trifluoromethoxy-benzenesulfonamide****Step A: Synthesis of [2-(4-amino-piperidin-1-yl)-quinazolin-4-yl]-dimethyl-amine.**

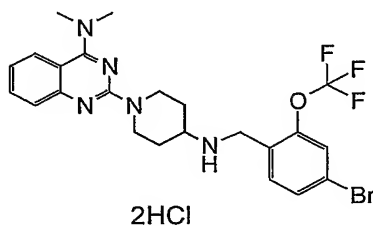
To a solution of 1-benzyl-piperidin-4-ylamine (2.00 g, 10.5 mmol) in THF (20 mL) was added (Boc)₂O (2.52 g, 11.5 mmol). The mixture was stirred at ambient temperature for 40 min, and concentrated. To a solution of the residue in MeOH (20 mL) was added 20% Pd(OH)₂ (400 mg). The mixture was stirred at ambient temperature under hydrogen atmosphere for 20 hr. Additionally, 20% Pd(OH)₂ (400 mg) was added and the mixture was stirred at ambient temperature under hydrogen atmosphere for 7 hr, at 50 °C for 4.5 hr, and at ambient temperature for 12 hr, filtered through a pad of celite, and concentrated to give a white solid. A mixture of (2-chloro-quinazolin-4-yl)-dimethyl-amine obtained in step B of example 1 (1.10 g, 5.30 mmol) and the above solid (1.27 g, 6.34 mmol) in 2-propanol (11 mL) was stirred at reflux for 20 hr. The precipitate was collected by filtration, washed with 2-propanol, dissolved in 50% MeOH in CHCl₃ (60 mL). The solution was poured into saturated aqueous NaHCO₃, and the aqueous layer was extracted with CHCl₃ (three times). The combined organic layer was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (NH-silica gel, EtOAc to CHCl₃) to give [2-(4-amino-piperidin-1-yl)-quinazolin-4-yl]-dimethyl-amine (864 mg, 68%) as a colorless oil. ESI MS m/e 272, M + H⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.79 (d, J = 8.2 Hz, 1 H), 7.45-7.55 (m, 2 H), 6.96-7.05 (m, 1 H), 4.83 (d, J = 13.4 Hz, 2 H), 3.26 (s, 6H), 2.84-3.03 (m, 3 H), 1.85-1.95 (m, 2 H), 1.20-1.50 (m, 4 H).

Step B: Synthesis of 4-bromo-N-[1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-yl]-2-trifluoromethoxy-benzenesulfonamide.

Using the procedure for the step A of example 20, the title compound was obtained.

ESI MS m/e 574, $M + H^+$; 1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, $J = 8.7$ Hz, 1 H), 7.80 (d, $J = 8.2$ Hz, 1 H), 7.39-7.61 (m, 4 H), 6.98-7.07 (m, 1 H), 4.60-4.81 (m, 3 H), 3.39-3.61 (m, 1 H), 3.25 (s, 6 H), 2.98-3.08 (m, 2 H), 1.73-1.92 (m, 2 H), 1.33-1.54 (m, 2 H).

Example 119



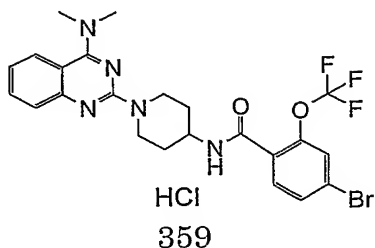
{2-[4-(4-Bromo-2-trifluoromethoxy-benzylamino)-piperidin-1-yl]-quinazolin-4-yl}-dimethyl-amine dihydrochloride

Step A: Synthesis of {2-[4-(4-bromo-2-trifluoromethoxy-benzylamino)-piperidin-1-yl]-quinazolin-4-yl}-dimethyl-amine dihydrochloride.

Using the procedure for the step B of example 37, the title compound was obtained.

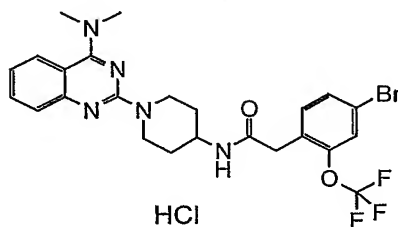
ESI MS m/e 524, M (free) + H^+ ; 1H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, $J = 8.1$ Hz, 1 H), 8.20 (d, $J = 8.4$ Hz, 1 H), 7.90 (d, $J = 8.4$ Hz, 1 H), 7.67 (t, $J = 7.5$ Hz, 1 H), 7.26-7.49 (m, 3 H), 5.13 (brs, 2 H), 4.27 (s, 2 H), 3.08-3.60 (s, 9 H), 2.08-2.78 (m, 4 H).

Example 120



4-Bromo-*N*-[1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-yl]-2-trifluoromethoxy-benzamide hydrochloride**Step A: Synthesis of 4-bromo-*N*-[1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-yl]-2-trifluoromethoxy-benzamide hydrochloride.**

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 560, M (free) Na⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.68 (s, 1 H), 8.73 (d, *J* = 7.8 Hz, 1 H), 7.80-7.91 (m, 2 H), 7.68 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1 H), 7.55 (dd, *J* = 8.4, 1.9 Hz, 1 H), 7.42-7.46 (m, 1 H), 7.29 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1 H), 6.67 (d, *J* = 7.3 Hz, 1 H), 5.04 (brs, 2 H), 4.23-4.42 (m, 1 H), 3.27-3.61 (m, 8 H), 2.19-2.36 (m, 2 H), 1.57-1.81 (m, 2 H).

Example 121**2-(4-Bromo-2-trifluoromethoxy-phenyl)-*N*-[1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-yl]-acetamide hydrochloride****Step A: Synthesis of 2-(4-bromo-2-trifluoromethoxy-phenyl)-*N*-[1-(4-dimethylamino-quinazolin-2-yl)-piperidin-4-yl]-acetamide hydrochloride.**

Using the procedure for the step A of example 47, the title compound was obtained. ESI MS *m/e* 574, M (free) + Na⁺; ¹H NMR (300 MHz, CDCl₃) δ 13.08 (s, 1 H), 8.61 (d, *J* = 8.4 Hz, 1 H), 7.86 (d, *J* = 7.5 Hz, 1 H), 7.56-7.68 (m, 2 H), 7.21-7.39 (m, 4 H), 4.70-5.10 (m, 2 H), 4.04-4.22 (m, 1 H), 3.68 (s, 2 H), 3.34-3.61 (m, 8 H), 1.59-2.19 (m, 4 H).

Example 122 - 301.

To a solution of amine obtained in step A of example 15 (30 μmol) and pyridine (120 μmol) in CH₂Cl₂ (400 μL) was added an appropriate sulfonyl chloride (60 μmol) in

CH₂Cl₂ (200 μL) at 25 °C. After stirring at the same temperature for 20 hr, the reaction mixture was concentrated by a stream of dry N₂. To the residue was partitioned between CHCl₃ and saturated aqueous NH₄Cl. The aqueous layer was extracted with CHCl₃. The combined organic layers were dried over MgSO₄. After concentration by a stream of dry N₂, dry CH₂Cl₂ (600 μL) and PSA (300 μL) were added to the residue. After the stirring at 25 °C for 20 hr, the reaction mixture was filtrated and purified by flash chromatography (NH-silica gel, 33% MeOH in CHCl₃) to give the desired product.

Example 302 - 588.

To a solution of amine obtained in step C of example 9 or step A of example 64 (30 μmol) in CH₂Cl₂ (200 μL) were added poly(4-vinylpyridine) (75 μL) in CH₂Cl₂ (200 μL) and acid chloride (60 μmol) in CH₂Cl₂ (200 μL) at 25 °C. After stirring at the same temperature for 20 hr, the reaction mixture was filtered and concentrated by a stream of dry N₂. To the residue were added dry CH₂Cl₂ (600 μL) and PSA (300 μL). After the stirring at 25 °C for 20 hr, the reaction mixture was filtrated and purified by flash chromatography (NH-silica gel, 33% MeOH in CHCl₃) to give the desired product.

Example 589 - 1136.

To a solution of carboxylic acid (200 μL, 60 μmol) in CH₂Cl₂ (200 μL) were added 1-cyclohexyl-3-methylpolystyrene-carbodiimide (150 μL, 126 μmol) in CH₂Cl₂ (200 μL) and amine obtained in step C of example 9 or step A of example 64 (30 μmol) in CH₂Cl₂ (200 μL) at 25 °C. After stirring at the same temperature for 20 hr, the reaction mixture was filtered through NH-silica gel, and concentrated by a stream of dry N₂. To the residue were added dry CH₂Cl₂ (700 μL) and polystyrene linked benzaldehyde (75 μL, 60 μmol). After the stirring at 50 °C for 20 hr, the reaction mixture was filtrated, and concentrated by a stream of dry N₂ to give the desired product.

Example 1137 - 1745.

To a solution of the amide product in THF (200 μl) was added 1 M borane-THF

complex in THF (300 μ l, 300 μ mol). The mixture was stirred at 80 °C for 1 hr, and concentrated by a stream of dry N₂. To the residue were added 1 M aqueous HCl (300 μ l) and THF (300 μ l). The mixture was stirred at 80 °C for 1 hr, and concentrated by a stream of dry N₂. To the residue was partitionated between CHCl₃ and 2 M aqueous sodium hydroxide. The aqueous layer was extracted with CHCl₃. The combined organic layers were dried over MgSO₄. The mixture was concentrated by a stream of dry N₂, and the purified by flash chromatography (silica gel, 2% to 7% 2 M NH₃/MeOH in CHCl₃) to give the desired product.

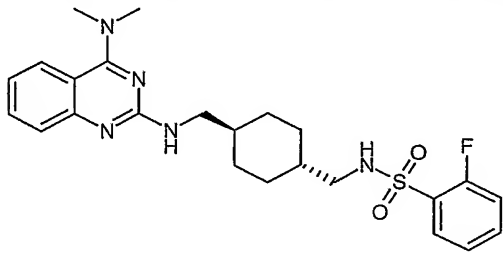
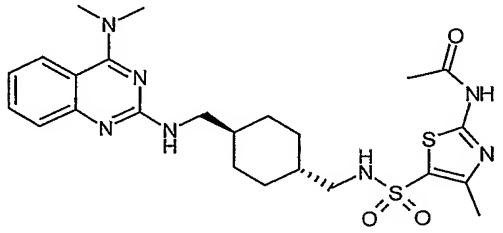
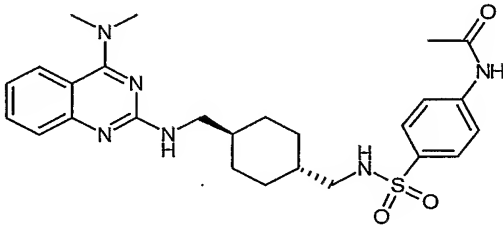
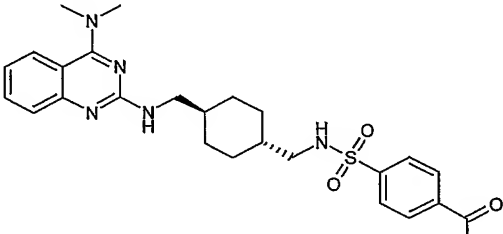
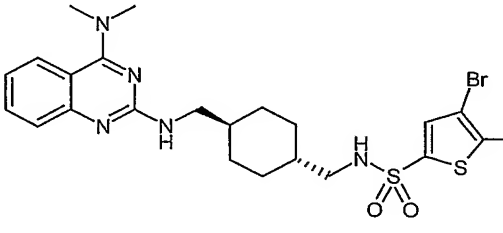
Example 1746 - 2184.

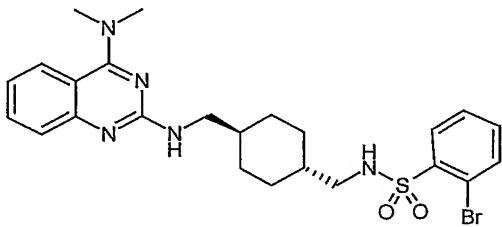
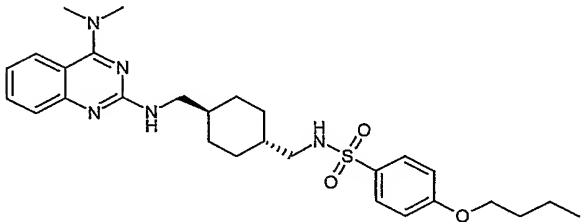
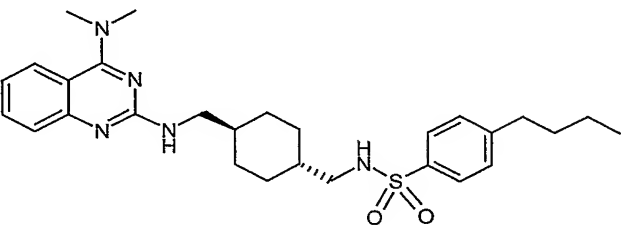
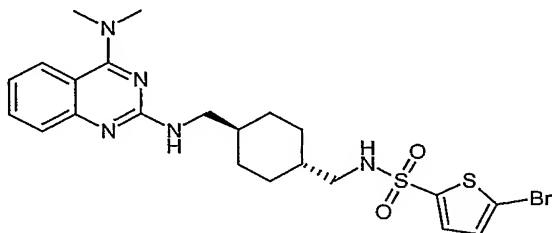
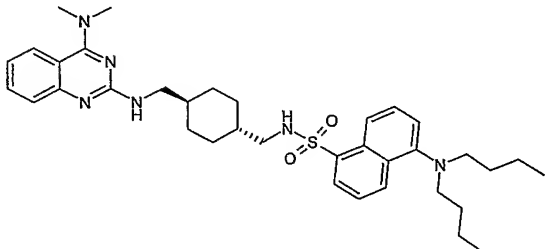
To a solution of amine obtained in step C of example 9 or step A of example 64 (36 μ mol) in MeOH (200 μ L) were added aldehyde (30 μ mol) in MeOH (200 μ L) and AcOH (90 μ mol) at 25 °C. The reaction mixture was stirred at the same temperature for 1 hr. To the mixture was added NaBH₃CN (120 μ mol) in MeOH (200 μ L). After stirring at the same temperature for 20 hr, the reaction mixture was concentrated by a stream of dry N₂. To the residue was partitionated between CHCl₃ and 2 M aqueous sodium hydroxide. The aqueous layer was extracted with CHCl₃. The combined organic layers were dried over MgSO₄. The mixture was concentrated by a stream of dry N₂, and purified by flash chromatography (silica gel, 2% to 7% 2 M NH₃/MeOH in CHCl₃) to give the desired product.

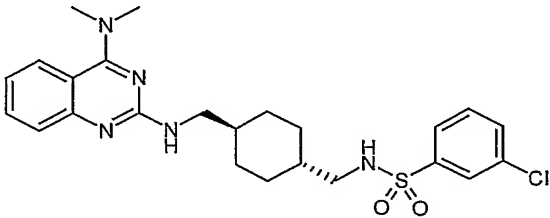
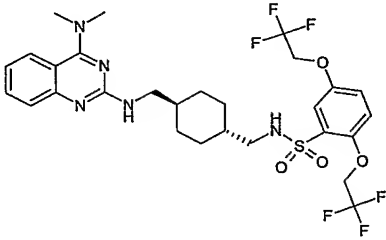
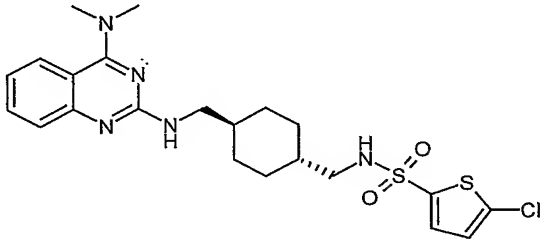
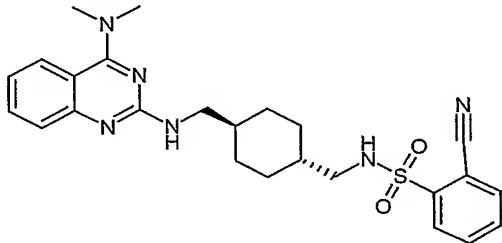
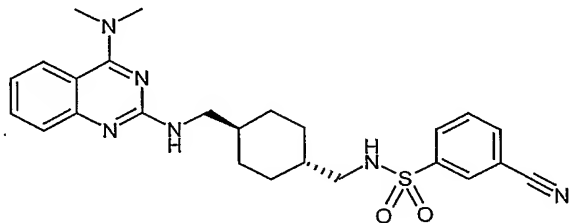
Example 2185 - 2328.

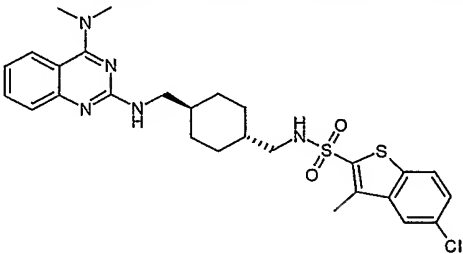
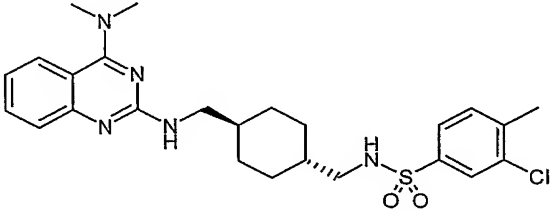
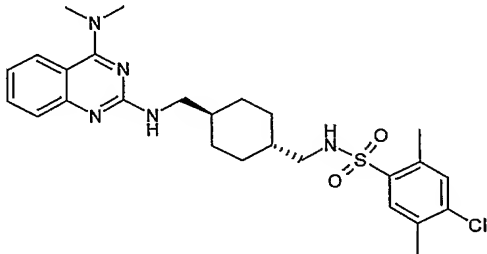
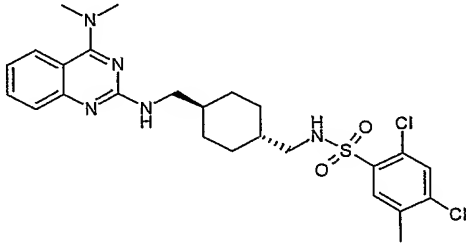
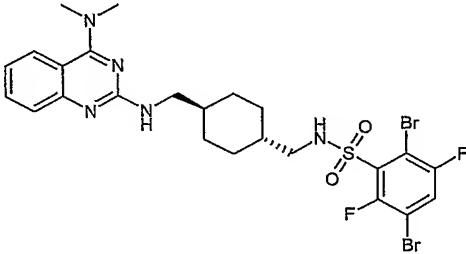
To a solution of alcohol (35 μ mol) in CH₂Cl₂ (200 μ L) was added Dess-Martin periodinane (63 μ mol) in CH₂Cl₂ (200 μ L) at 25 °C, and the reaction mixture was stirred at the same temperature for 20 hr. To the reaction mixture were added amine obtained in step C of example 9 or step A of example 64 (36 μ mol) in MeOH (200 μ L) and AcOH (90 μ L), and the mixture was stirred at the same temperature for 1 hr. To the mixture was added NaBH₃CN (120 μ mol) in MeOH (200 μ L). After stirring at the same temperature for 20 hr, the reaction mixture was concentrated by a stream of dry N₂. To the residue was partitionated between CHCl₃ and 2 M aqueous sodium hydroxide. The aqueous layer was

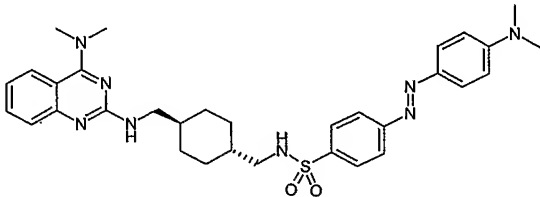
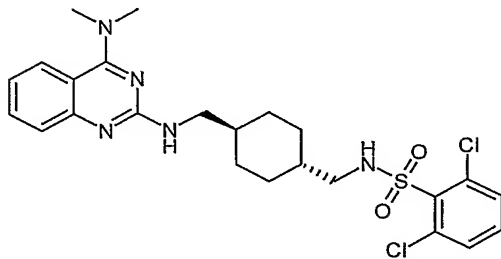
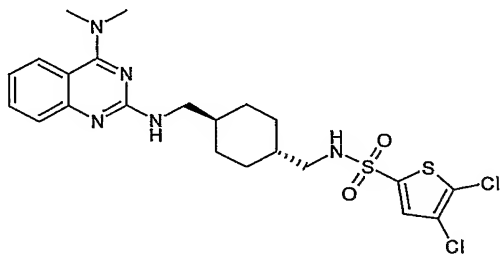
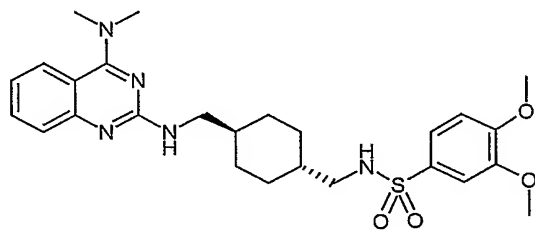
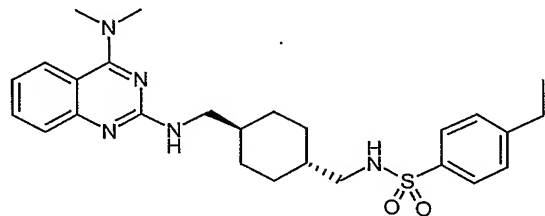
extracted with CHCl_3 . The combined organic layers were dried over MgSO_4 . The mixture was concentrated by a stream of dry N_2 , and purified by flash chromatography (silica gel, 2% to 7% 2 M NH_3/MeOH in CHCl_3) to give the desired product.

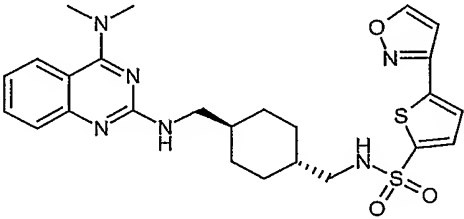
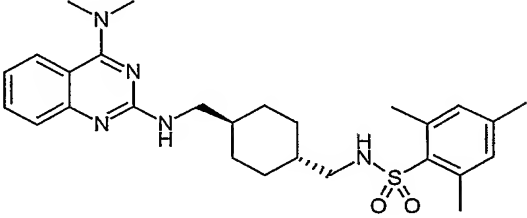
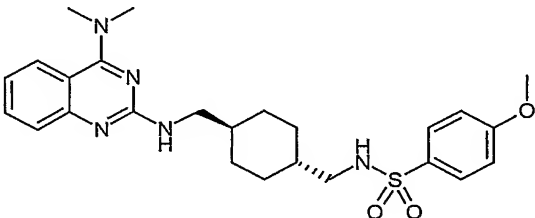
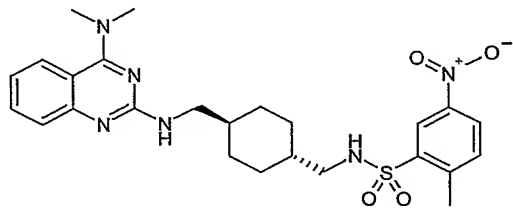
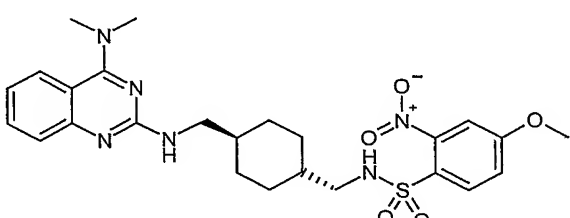
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 122 |  | 472 (M + H) |
| 123 |  | 532 (M + H) |
| 124 |  | 511 (M + H) |
| 125 |  | 496 (M + H) |
| 126 |  | 616 (M + H) |

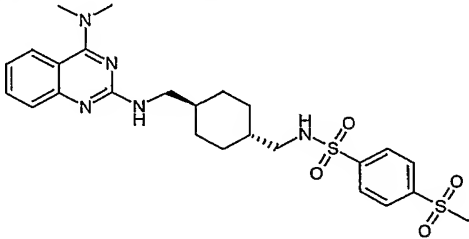
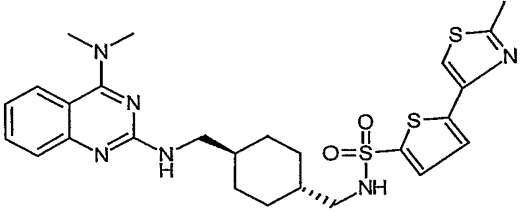
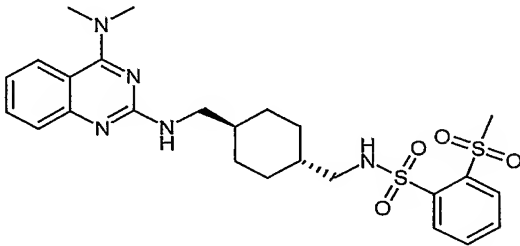
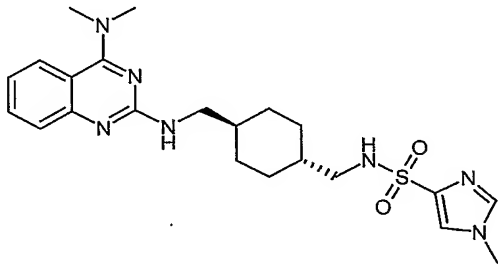
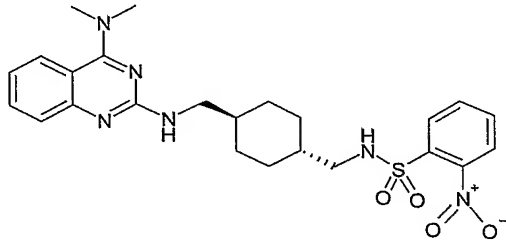
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 127 |  | 532 (M + H) |
| 128 |  | 526 (M + H) |
| 129 |  | 510 (M + H) |
| 130 |  | 538 (M + H) |
| 131 |  | 631 (M + H) |

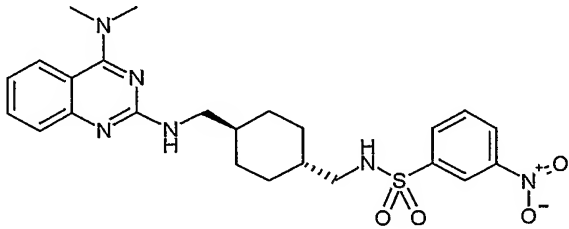
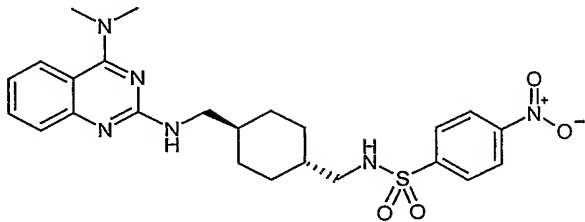
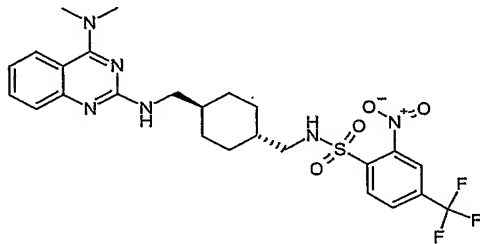
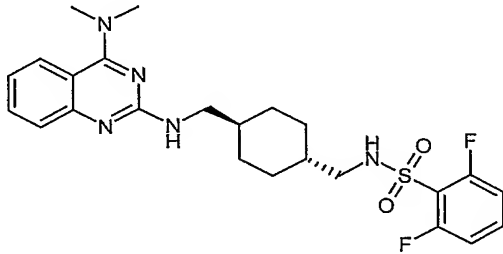
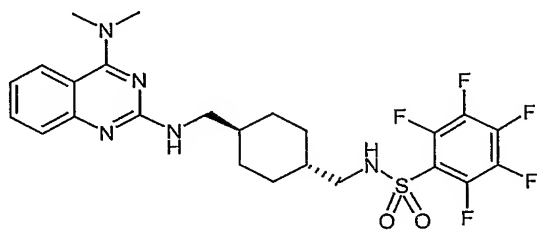
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 132 |  | 488 (M + H) |
| 133 |  | 650 (M + H) |
| 134 |  | 494 (M + H) |
| 135 |  | 479 (M + H) |
| 136 |  | 479 (M + H) |

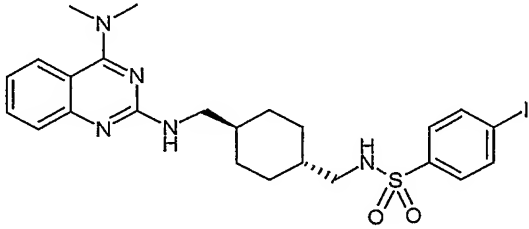
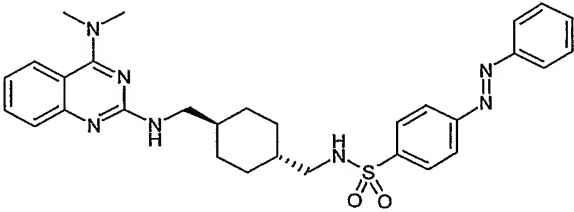
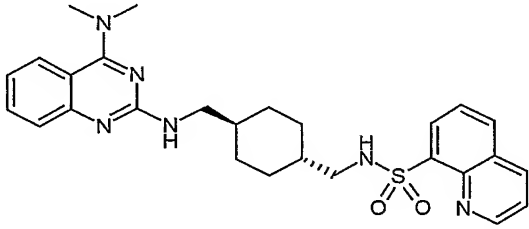
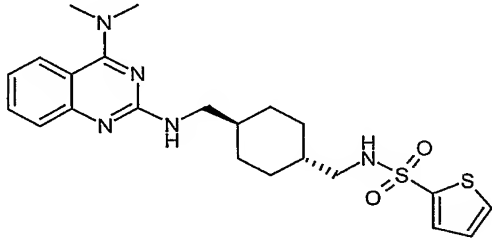
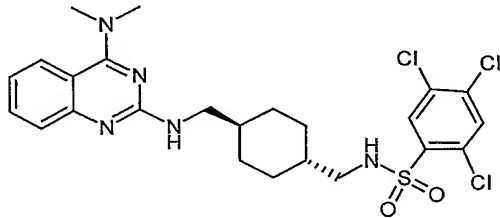
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 137 |  | 558 (M + H) |
| 138 |  | 502 (M + H) |
| 139 |  | 516 (M + H) |
| 140 |  | 536 (M + H) |
| 141 |  | 646 (M + H) |

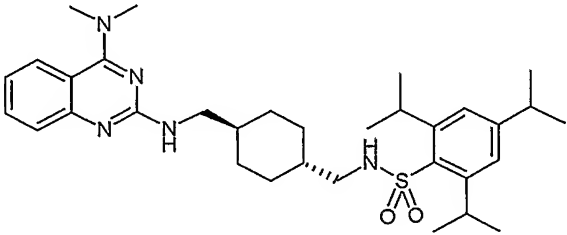
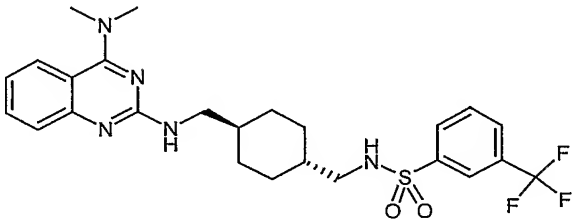
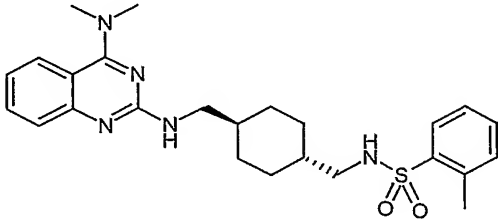
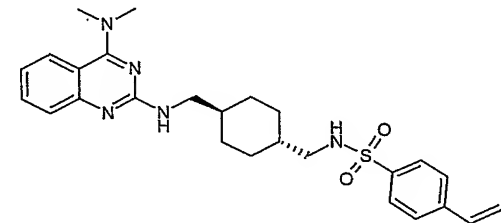
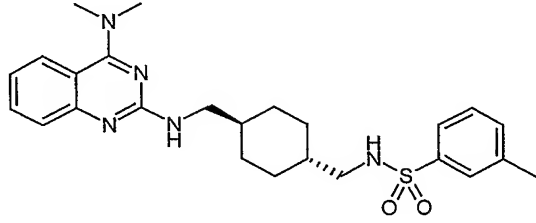
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 142 |  | 601 (M + H) |
| 143 |  | 522 (M + H) |
| 144 |  | 528 (M + H) |
| 145 |  | 514 (M + H) |
| 146 |  | 482 (M + H) |

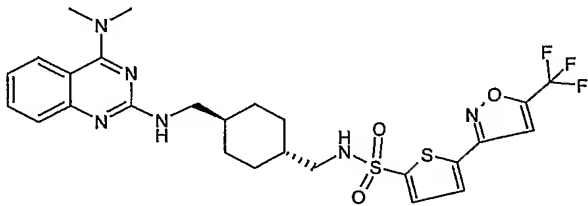
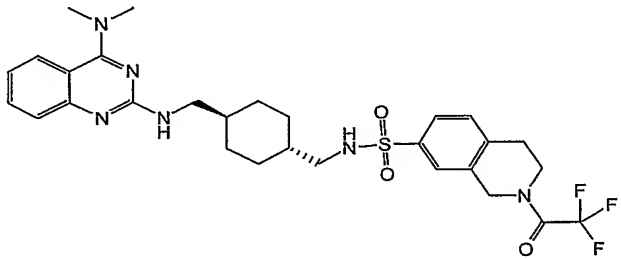
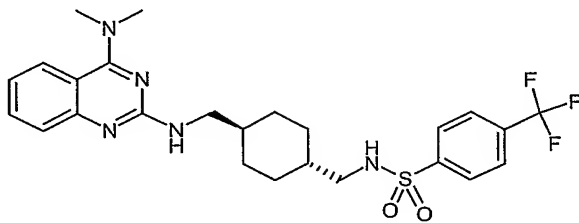
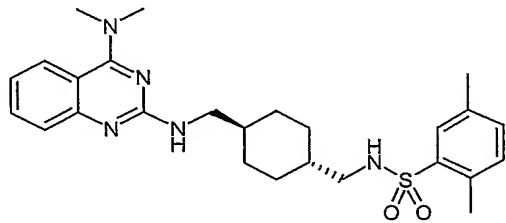
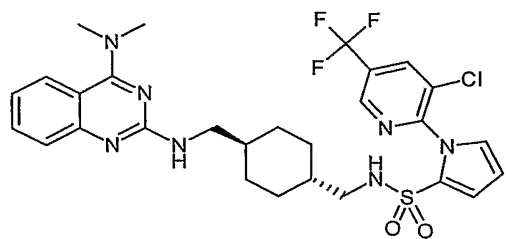
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 147 |  | 527 (M + H) |
| 148 |  | 496 (M + H) |
| 149 |  | 484 (M + H) |
| 150 |  | 513 (M + H) |
| 151 |  | 529 (M + H) |

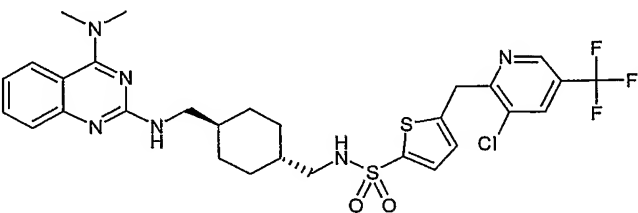
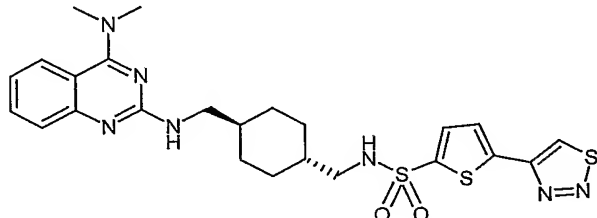
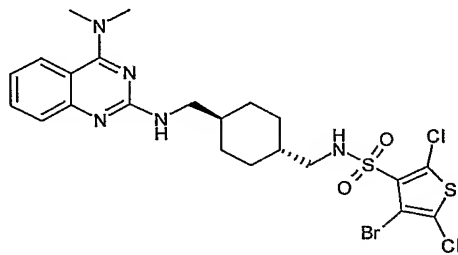
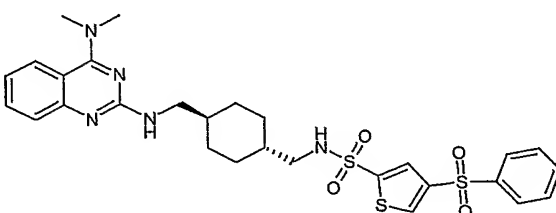
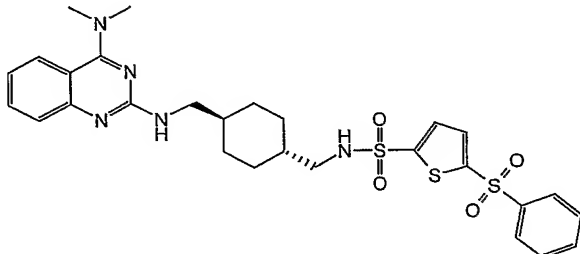
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 152 |  | 532 (M + H) |
| 153 |  | 557 (M + H) |
| 154 |  | 532 (M + H) |
| 155 |  | 458 (M + H) |
| 156 |  | 499 (M + H) |

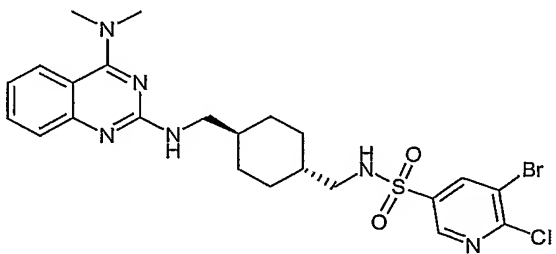
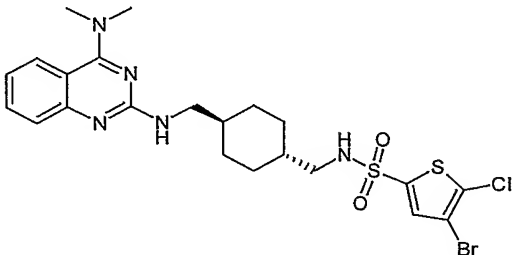
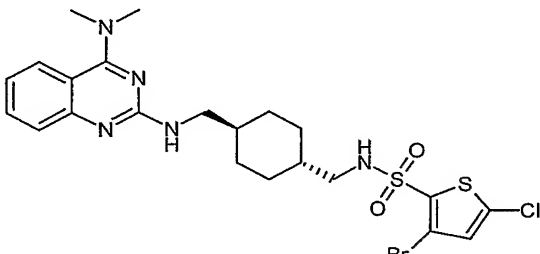
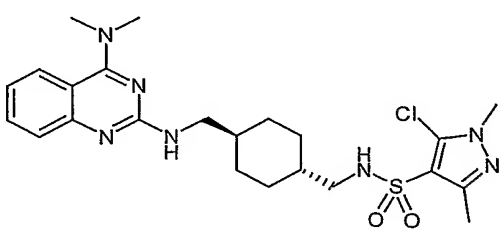
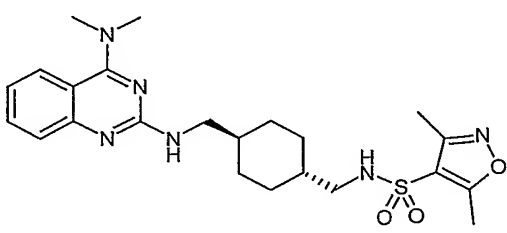
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 157 |  | 499 (M + H) |
| 158 |  | 499 (M + H) |
| 159 |  | 567 (M + H) |
| 160 |  | 490 (M + H) |
| 161 |  | 544 (M + H) |

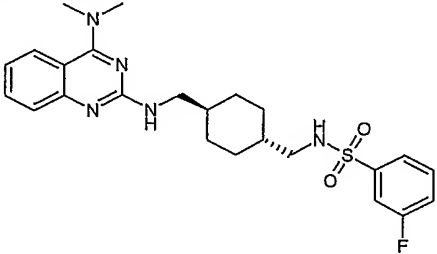
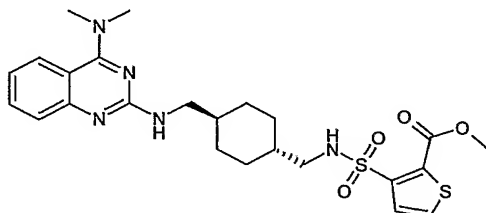
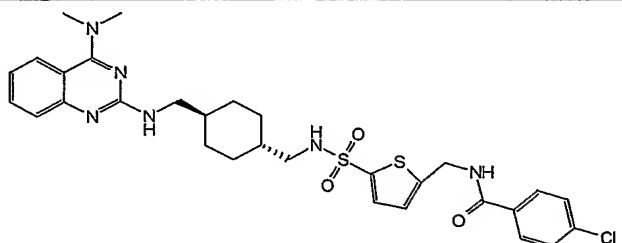
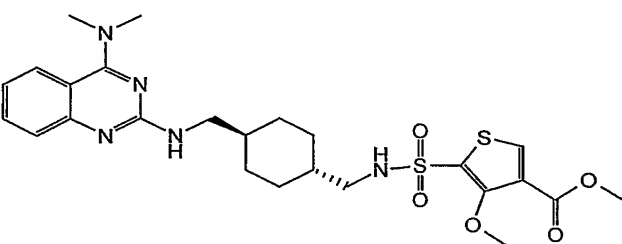
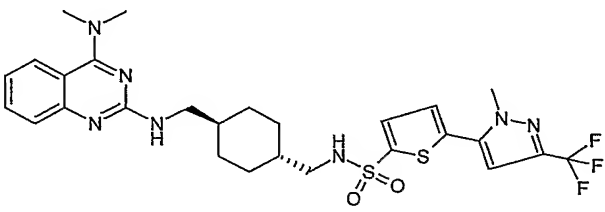
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 162 |  | 580 (M + H) |
| 163 |  | 558 (M + H) |
| 164 |  | 505 (M + H) |
| 165 |  | 460 (M + H) |
| 166 |  | 556 (M + H) |

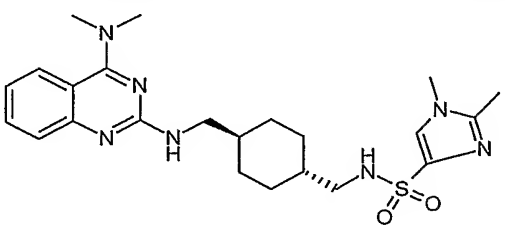
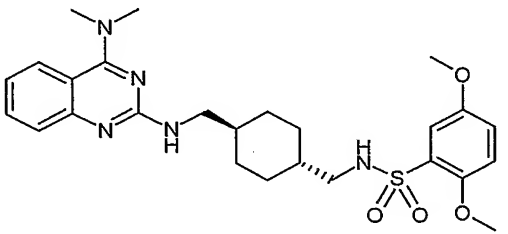
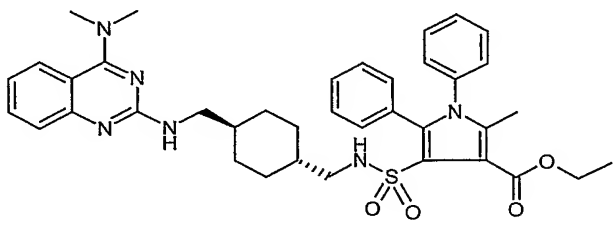
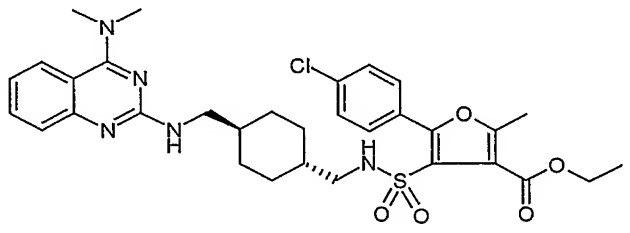
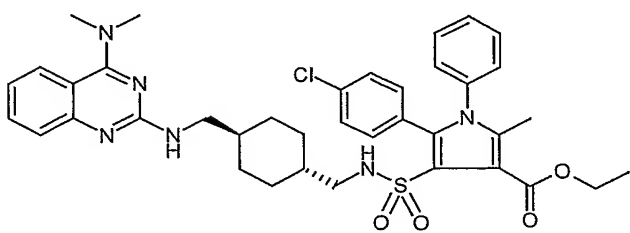
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 167 |  | 580 (M + H) |
| 168 |  | 522 (M + H) |
| 169 |  | 468 (M + H) |
| 170 |  | 480 (M + H) |
| 171 |  | 468 (M + H) |

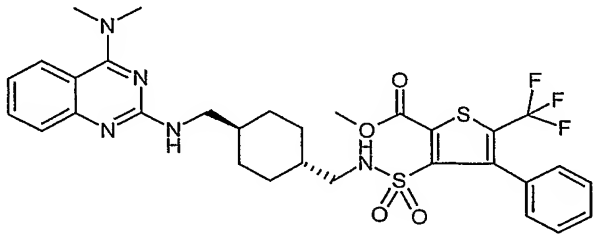
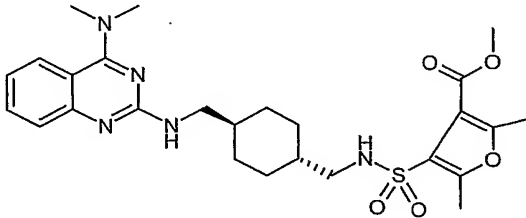
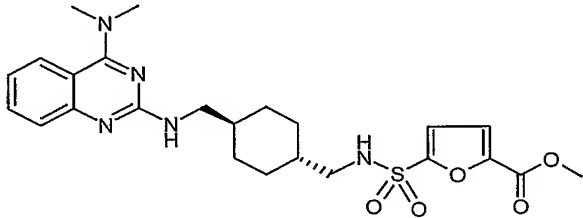
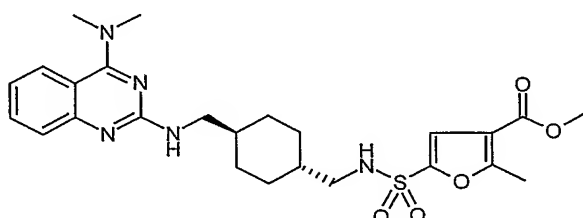
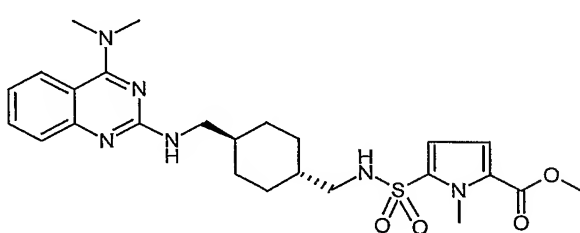
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 172 |  | 595 (M + H) |
| 173 |  | 605 (M + H) |
| 174 |  | 522 (M + H) |
| 175 |  | 482 (M + H) |
| 176 |  | 622 (M + H) |

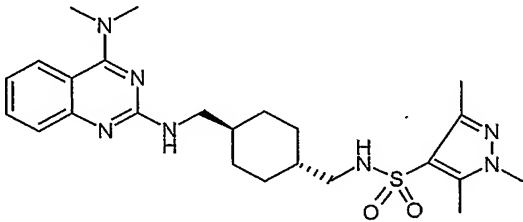
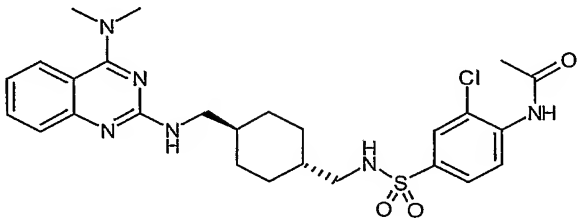
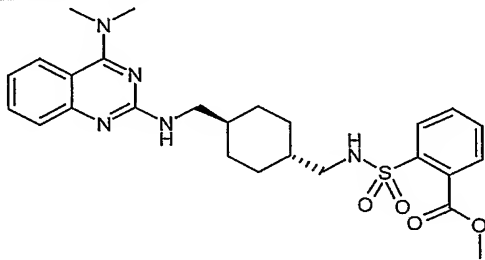
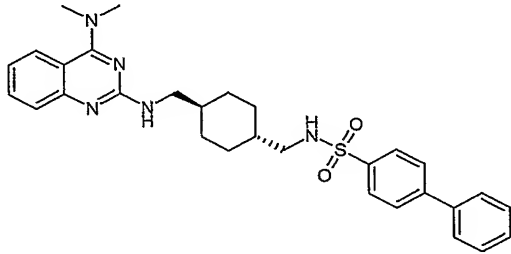
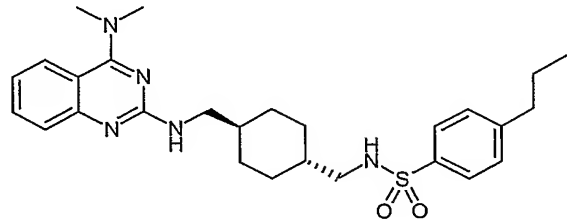
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 177 |  | 653 (M + H) |
| 178 |  | 544 (M + H) |
| 179 |  | 606 (M + H) |
| 180 |  | 600 (M + H) |
| 181 |  | 600 (M + H) |

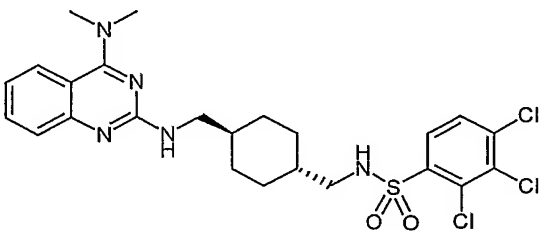
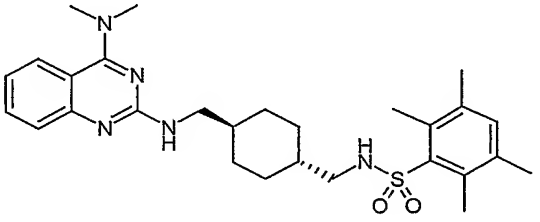
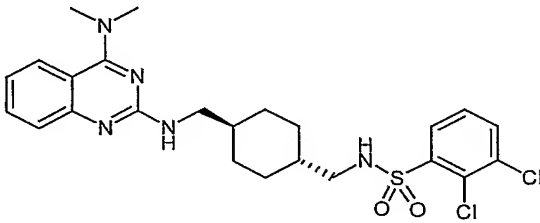
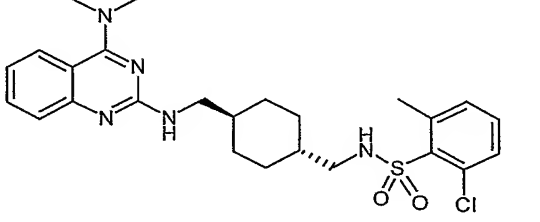
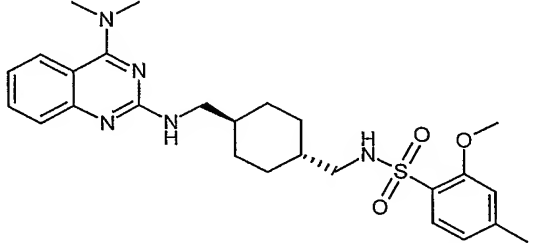
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 182 |  | 567 (M + H) |
| 183 |  | 572 (M + H) |
| 184 |  | 572 (M + H) |
| 185 |  | 506 (M + H) |
| 186 |  | 473 (M + H) |

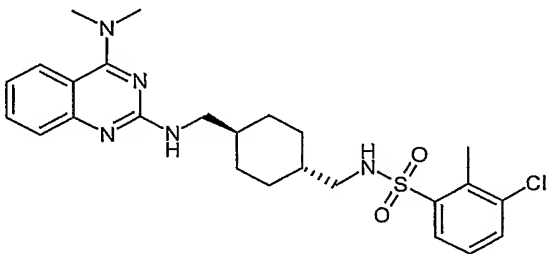
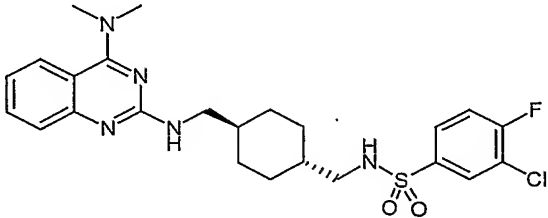
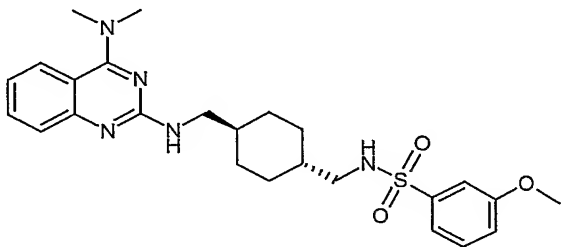
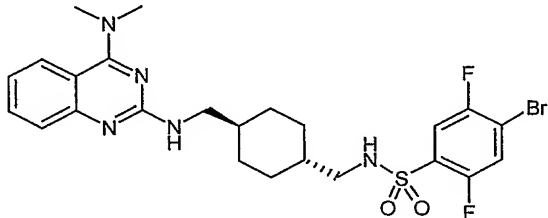
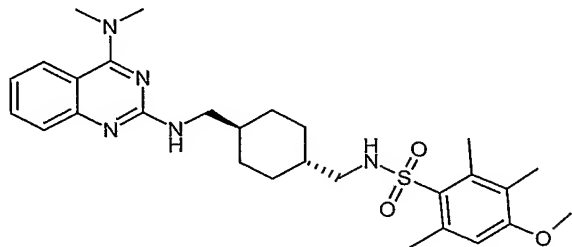
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 187 |  | 472 (M + H) |
| 188 |  | 518 (M + H) |
| 189 |  | 627 (M + H) |
| 190 |  | 548 (M + H) |
| 191 |  | 608 (M + H) |

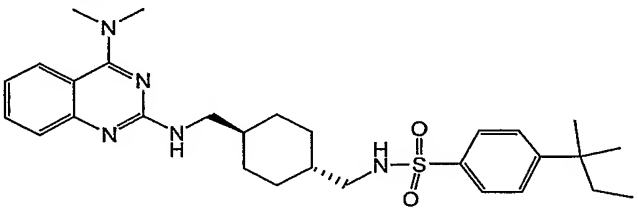
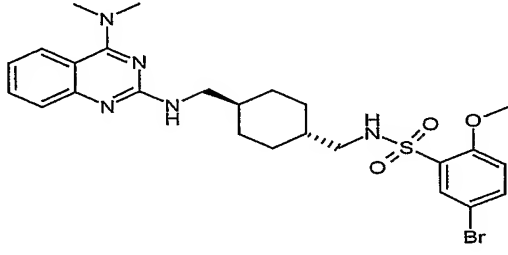
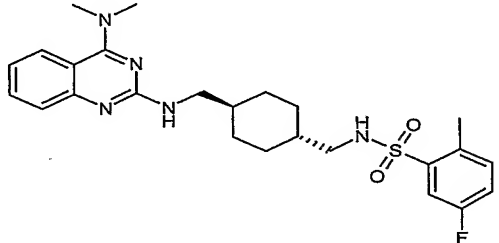
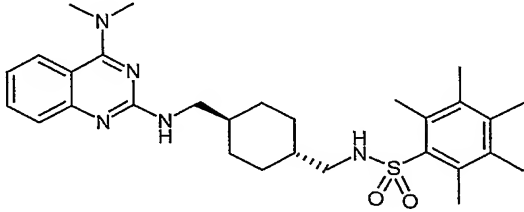
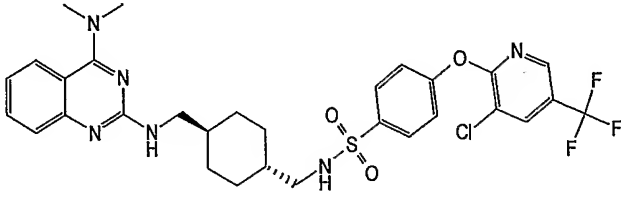
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 192 |  | 472 (M + H) |
| 193 |  | 514 (M + H) |
| 194 |  | 681 (M + H) |
| 195 |  | 640 (M + H) |
| 196 |  | 715 (M + H) |

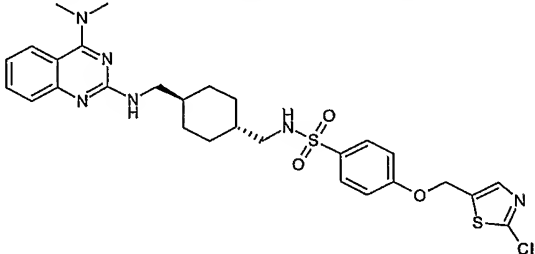
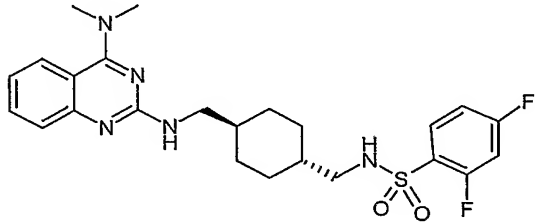
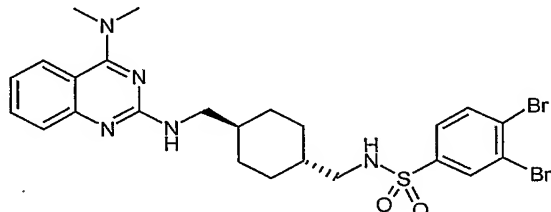
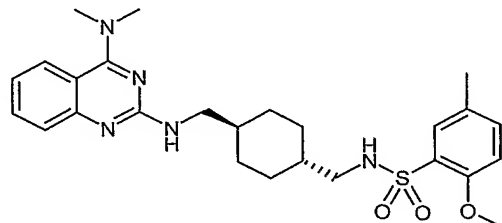
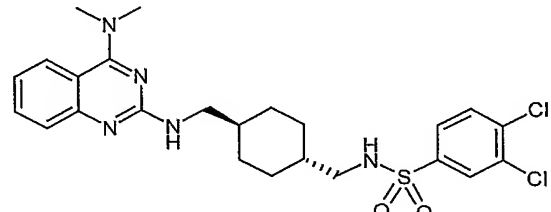
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 197 |  | 662 (M + H) |
| 198 |  | 530 (M + H) |
| 199 |  | 502 (M + H) |
| 200 |  | 516 (M + H) |
| 201 |  | 515 (M + H) |

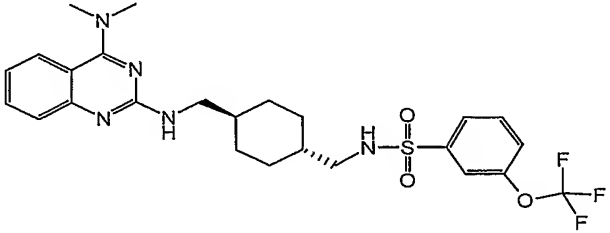
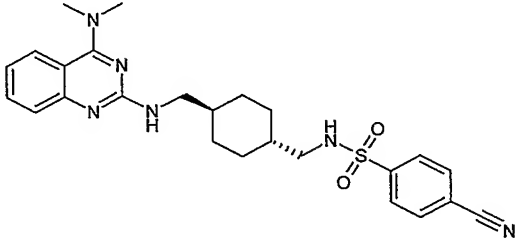
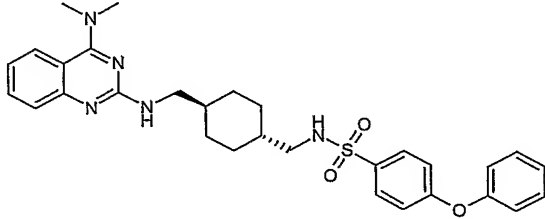
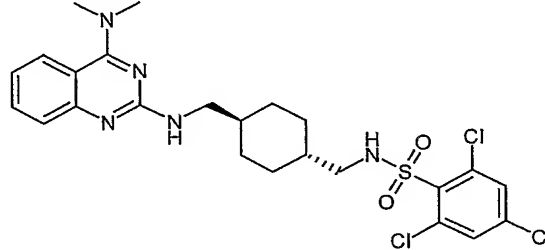
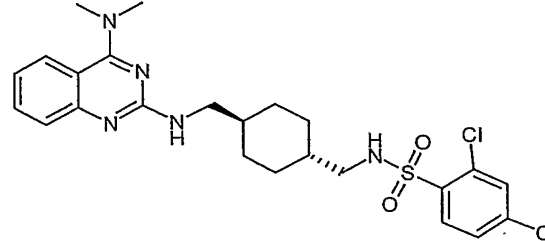
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 202 |  | 486 (M + H) |
| 203 |  | 545 (M + H) |
| 204 |  | 512 (M + H) |
| 205 |  | 530 (M + H) |
| 206 |  | 496 (M + H) |

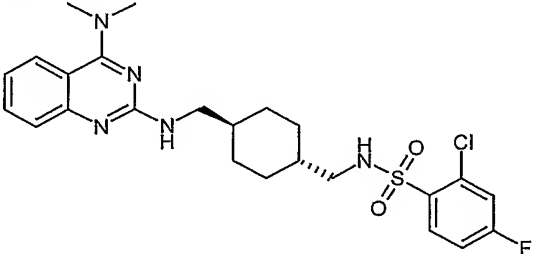
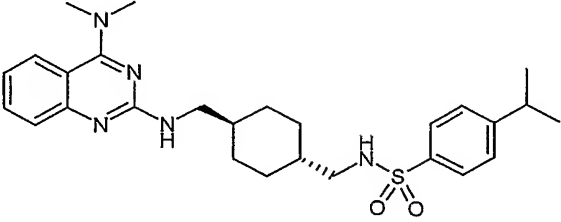
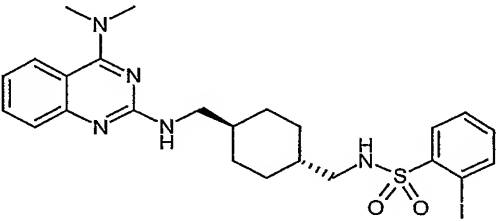
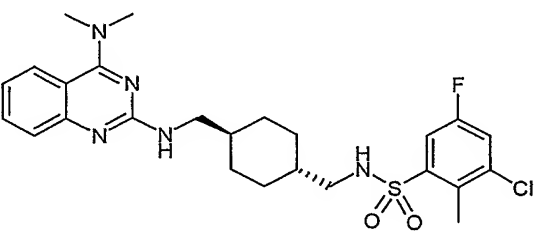
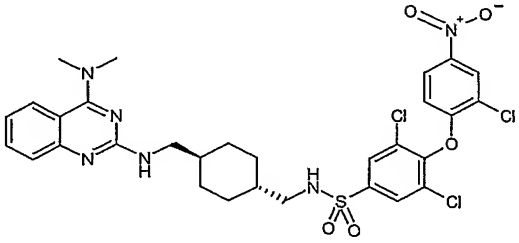
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 207 |  | 556 (M + H) |
| 208 |  | 510 (M + H) |
| 209 |  | 522 (M + H) |
| 210 |  | 502 (M + H) |
| 211 |  | 498 (M + H) |

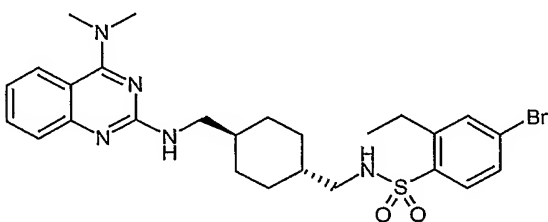
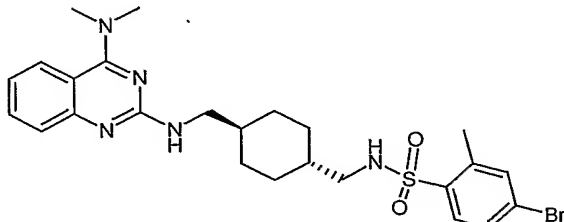
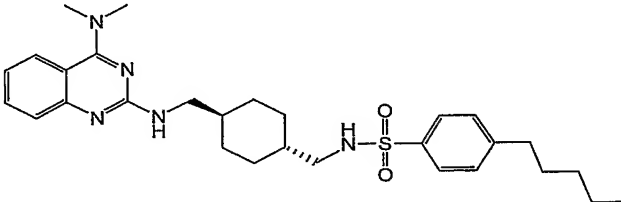
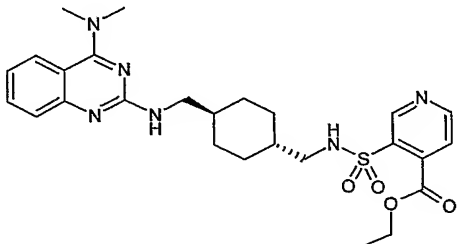
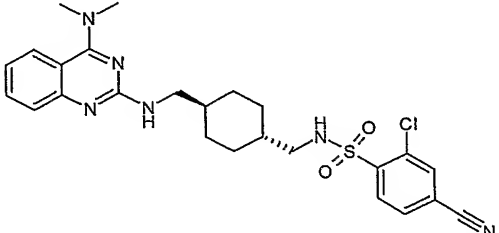
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 212 |  | 502 (M + H) |
| 213 |  | 506 (M + H) |
| 214 |  | 484 (M + H) |
| 215 |  | 568 (M + H) |
| 216 |  | 526 (M + H) |

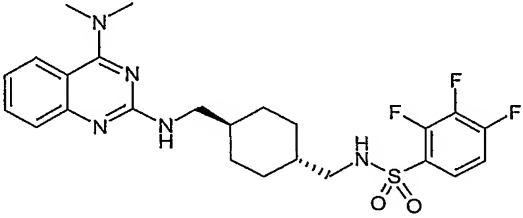
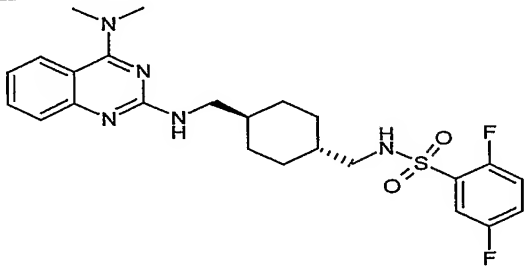
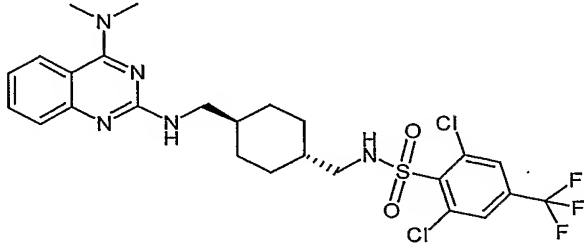
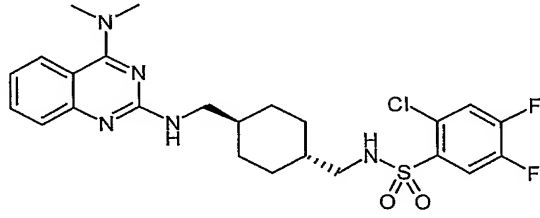
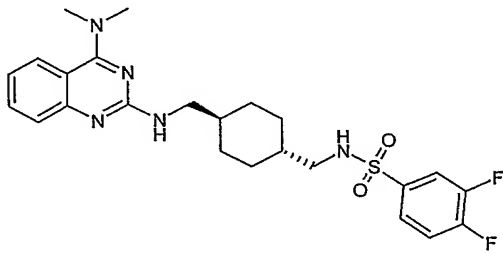
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 217 |  | 524 (M + H) |
| 218 |  | 562 (M + H) |
| 219 |  | 486 (M + H) |
| 220 |  | 524 (M + H) |
| 221 |  | 649 (M + H) |

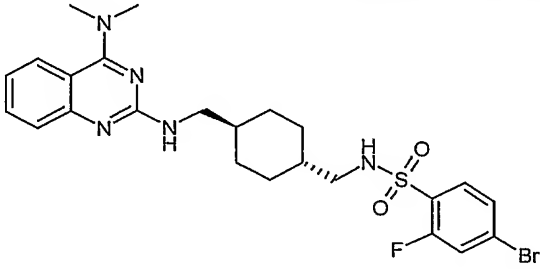
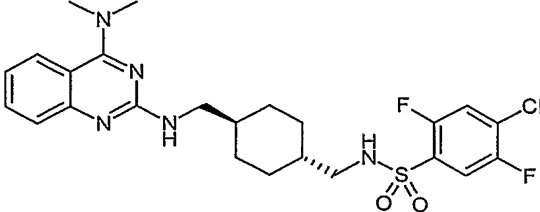
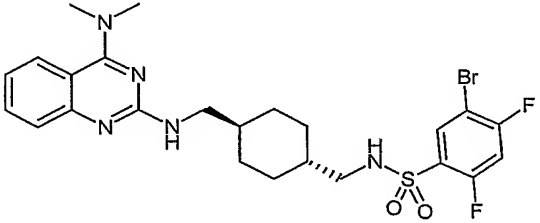
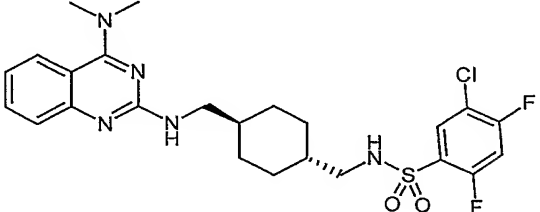
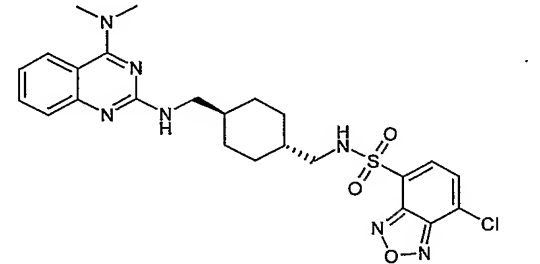
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 222 |  | 601 (M + H) |
| 223 |  | 490 (M + H) |
| 224 |  | 610 (M + H) |
| 225 |  | 498 (M + H) |
| 226 |  | 522 (M + H) |

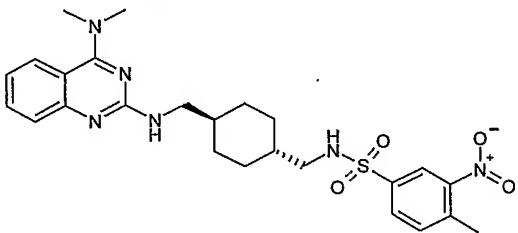
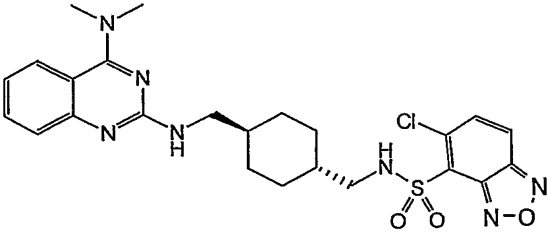
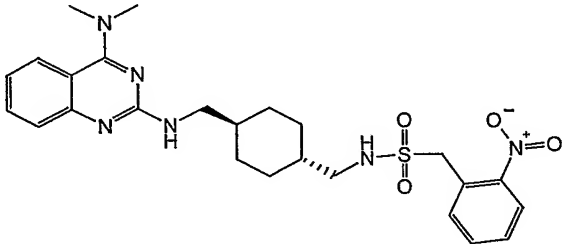
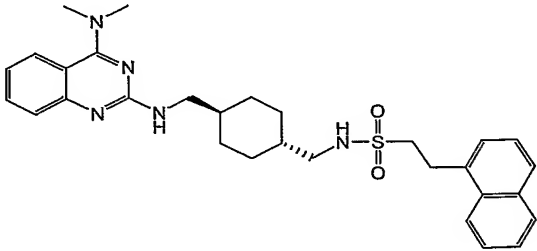
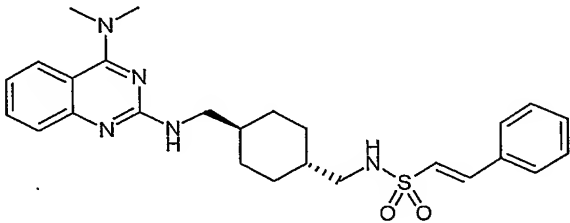
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 227 |  | 538 (M + H) |
| 228 |  | 479 (M + H) |
| 229 |  | 546 (M + H) |
| 230 |  | 556 (M + H) |
| 231 |  | 522 (M + H) |

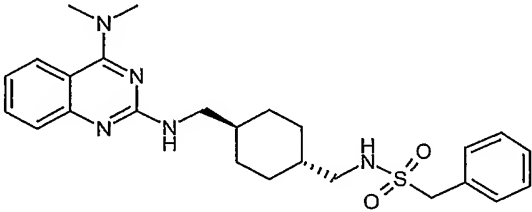
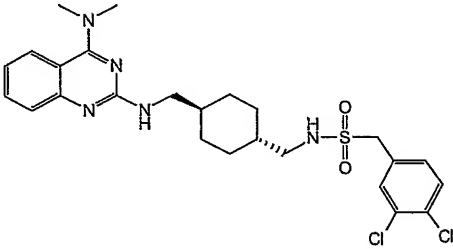
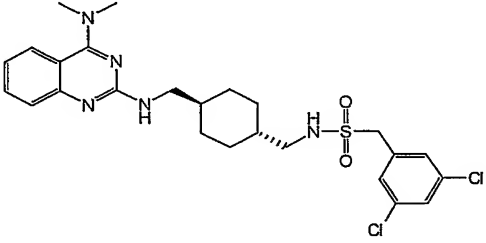
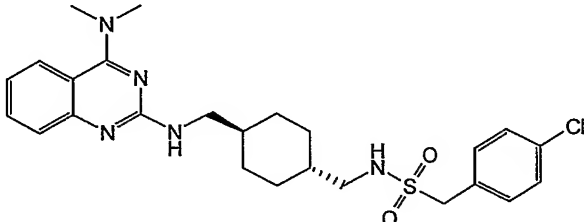
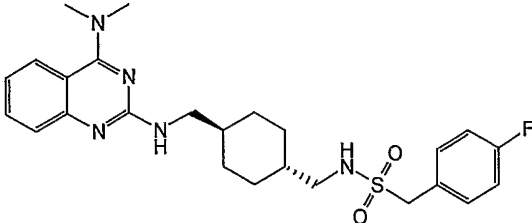
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 232 |  | 506 (M + H) |
| 233 |  | 496 (M + H) |
| 234 |  | 580 (M + H) |
| 235 |  | 520 (M + H) |
| 236 |  | 693 (M + H) |

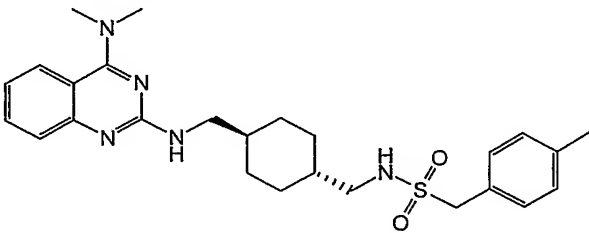
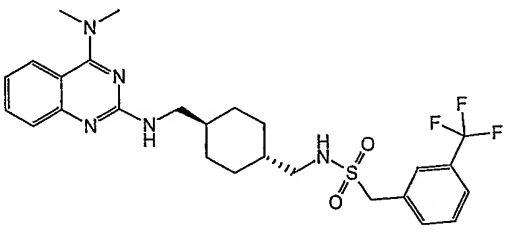
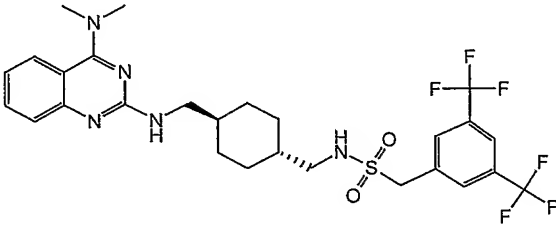
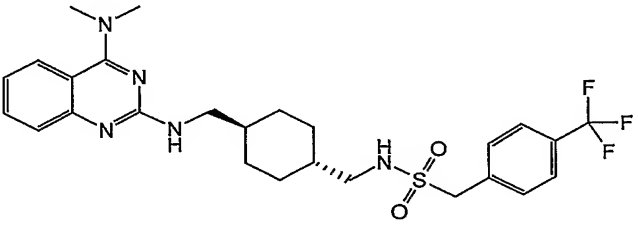
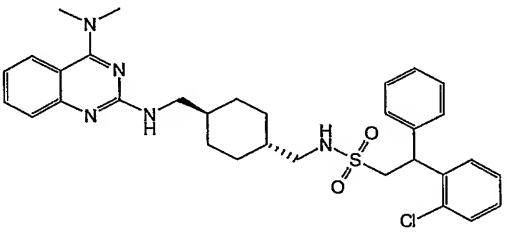
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 237 |  | 560 (M + H) |
| 238 |  | 546 (M + H) |
| 239 |  | 524 (M + H) |
| 240 |  | 527 (M + H) |
| 241 |  | 513 (M + H) |

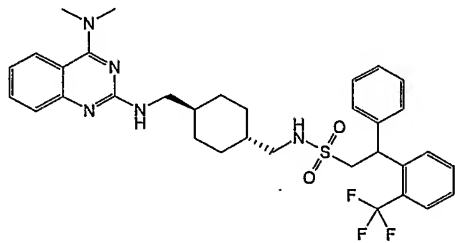
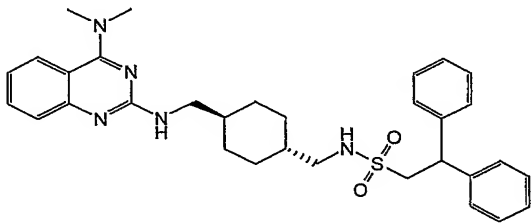
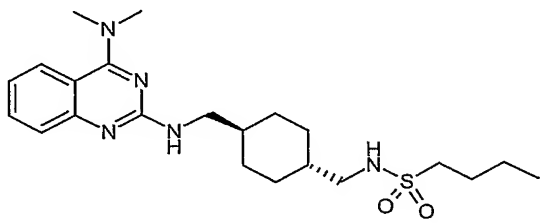
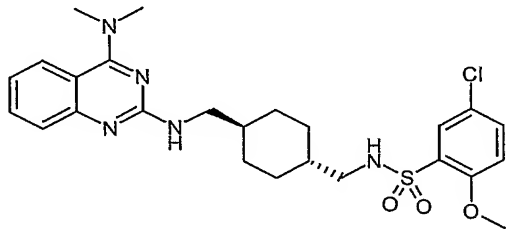
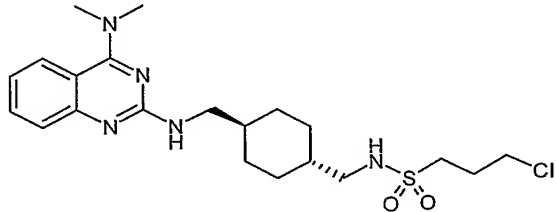
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 242 |  | 508 (M + H) |
| 243 |  | 490 (M + H) |
| 244 |  | 590 (M + H) |
| 245 |  | 524 (M + H) |
| 246 |  | 490 (M + H) |

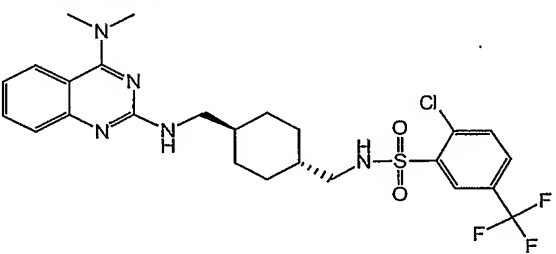
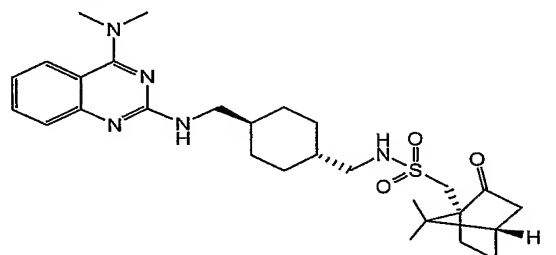
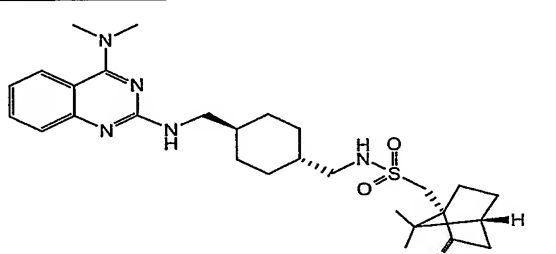
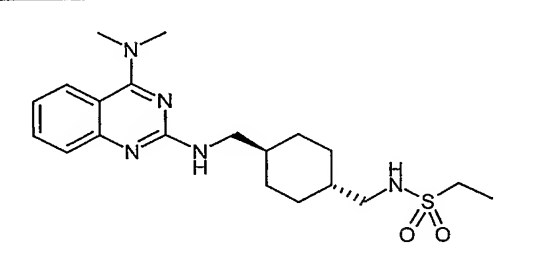
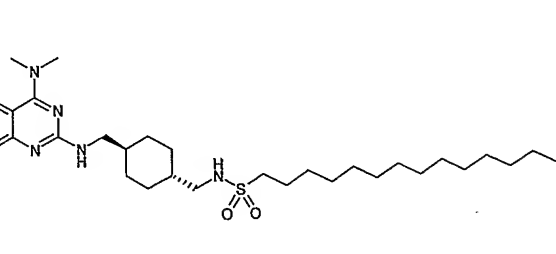
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 247 |  | 550 (M + H) |
| 248 |  | 524 (M + H) |
| 249 |  | 568 (M + H) |
| 250 |  | 524 (M + H) |
| 251 |  | 530 (M + H) |

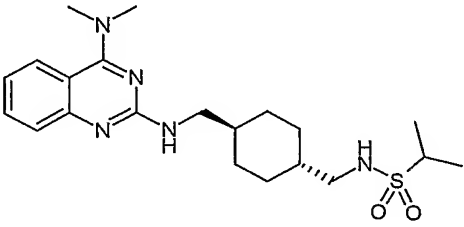
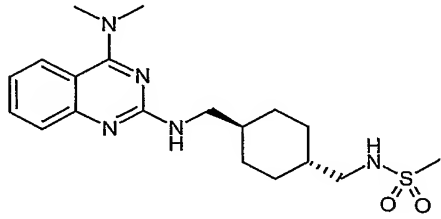
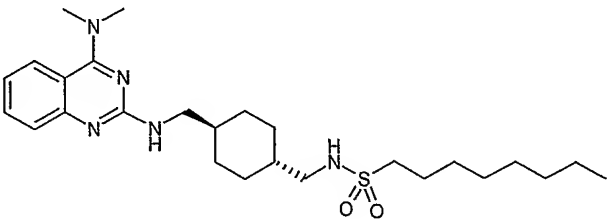
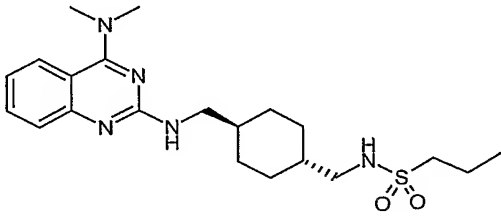
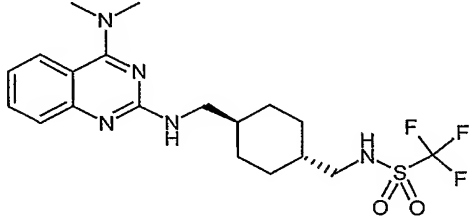
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 252 |  | 513 (M + H) |
| 253 |  | 530 (M + H) |
| 254 |  | 513 (M + H) |
| 255 |  | 532 (M + H) |
| 256 |  | 480 (M + H) |

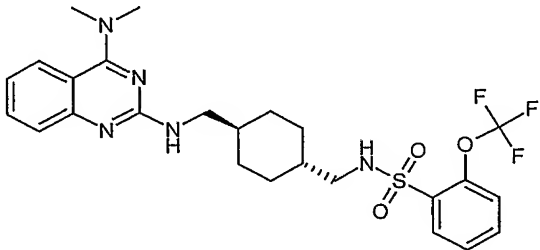
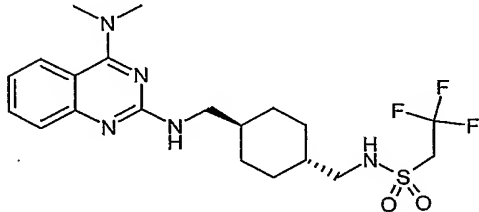
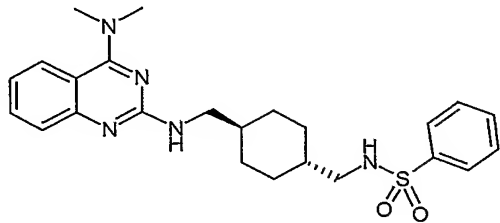
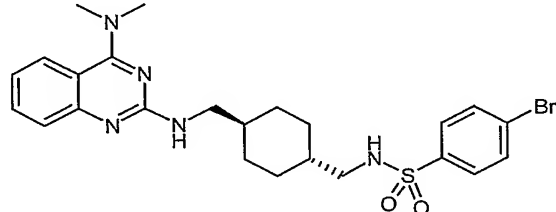
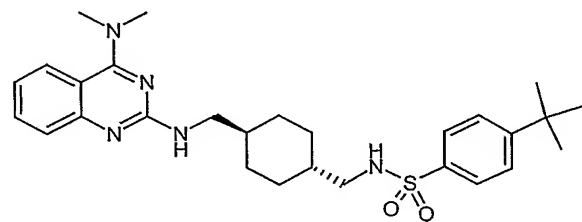
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 257 |  | 468 (M + H) |
| 258 |  | 536 (M + H) |
| 259 |  | 536 (M + H) |
| 260 |  | 502 (M + H) |
| 261 |  | 486 (M + H) |

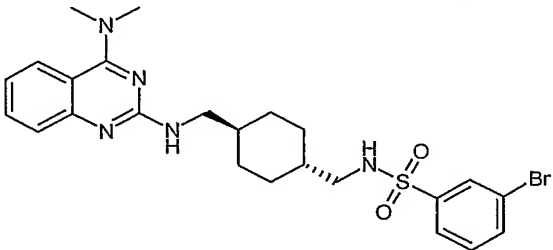
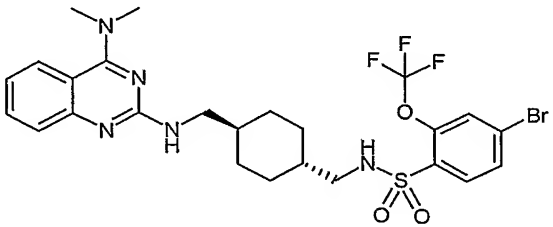
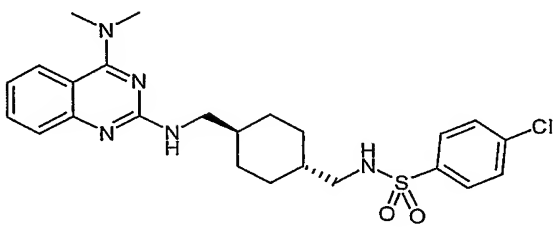
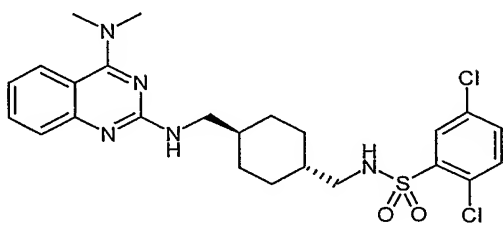
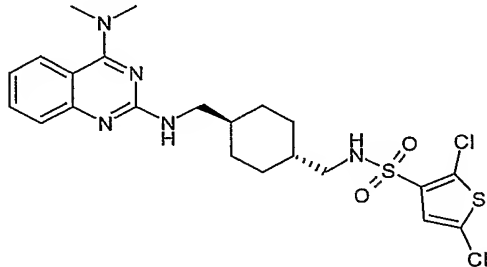
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 262 |  | 482 (M + H) |
| 263 |  | 536 (M + H) |
| 264 |  | 604 (M + H) |
| 265 |  | 536 (M + H) |
| 266 |  | 592 (M + H) |

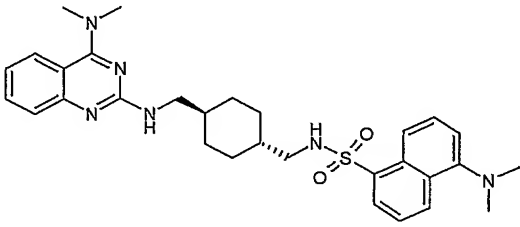
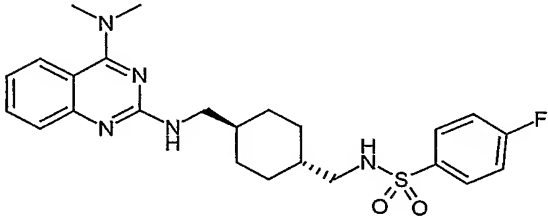
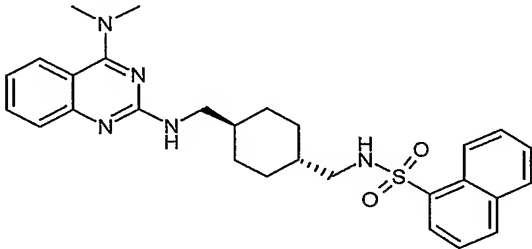
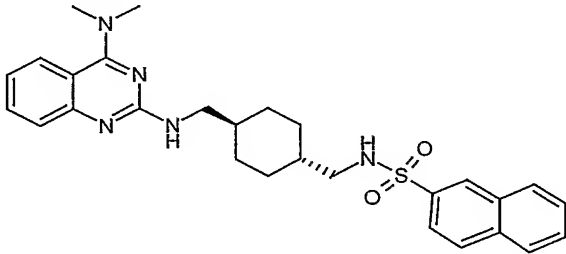
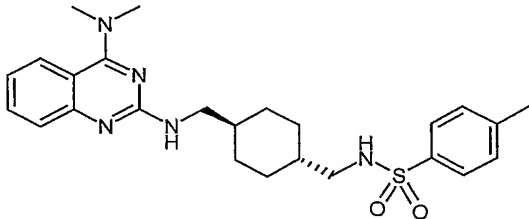
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 267 |  | 626 (M + H) |
| 268 |  | 558 (M + H) |
| 269 |  | 434 (M + H) |
| 270 |  | 518 (M + H) |
| 271 |  | 454 (M + H) |

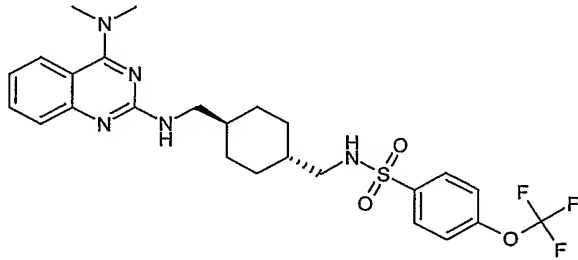
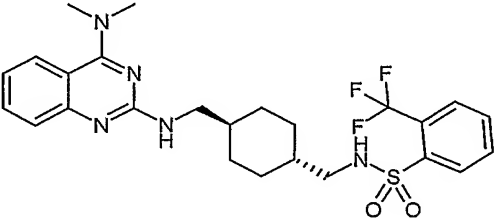
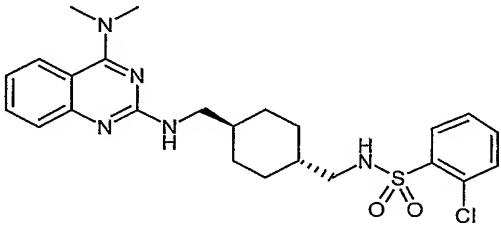
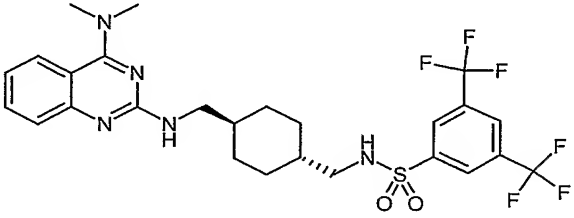
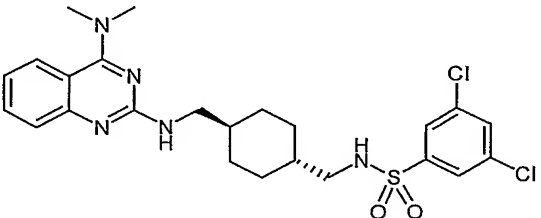
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 272 |  | 556 (M + H) |
| 273 |  | 528 (M + H) |
| 274 |  | 528 (M + H) |
| 275 |  | 406 (M + H) |
| 276 |  | 602 (M + H) |

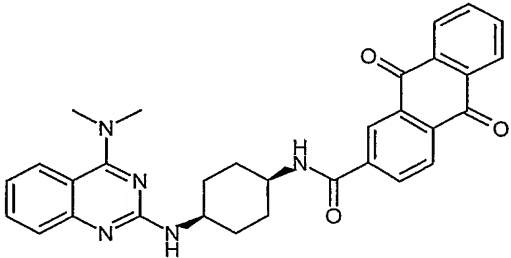
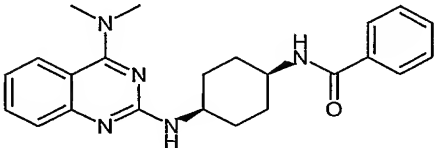
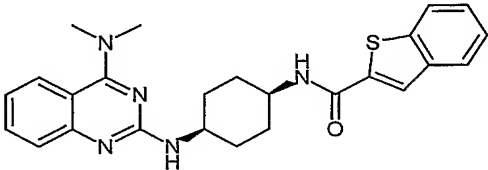
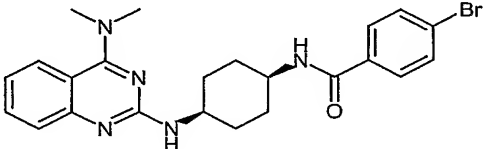
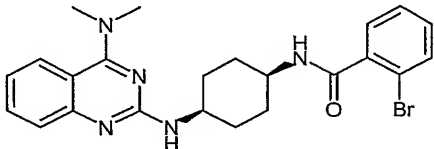
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 277 |  | 420 (M + H) |
| 278 |  | 392 (M + H) |
| 279 |  | 490 (M + H) |
| 280 |  | 420 (M + H) |
| 281 |  | 446 (M + H) |

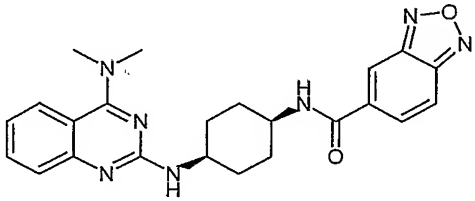
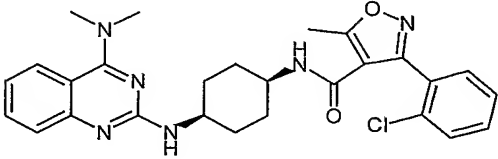
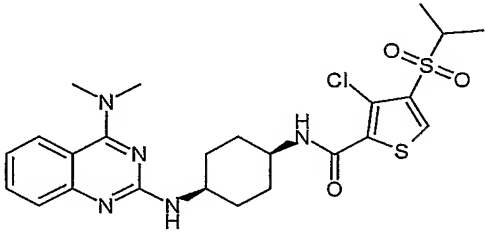
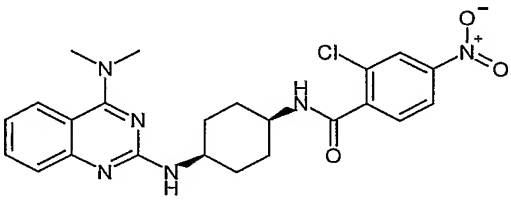
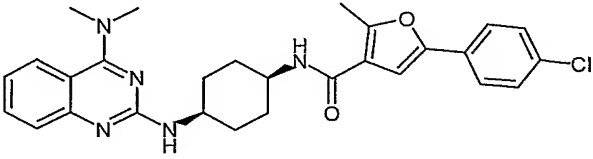
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 282 |  | 538 (M + H) |
| 283 |  | 460 (M + H) |
| 284 |  | 454 (M + H) |
| 285 |  | 532 (M + H) |
| 286 |  | 510 (M + H) |

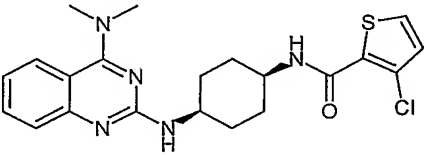
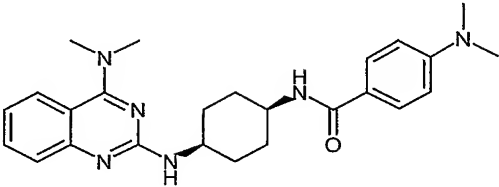
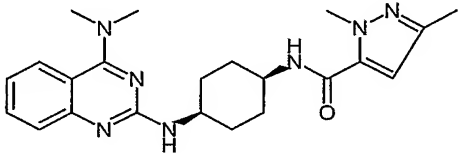
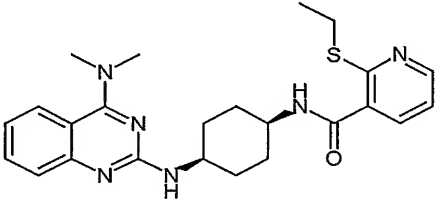
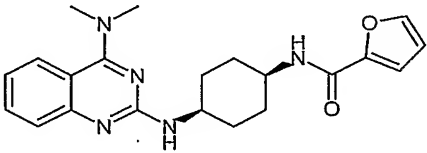
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 287 |  | 532 (M + H) |
| 288 |  | 616 (M + H) |
| 289 |  | 488 (M + H) |
| 290 |  | 522 (M + H) |
| 291 |  | 528 (M + H) |

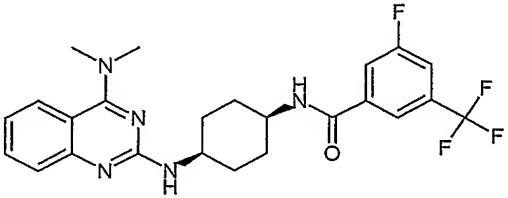
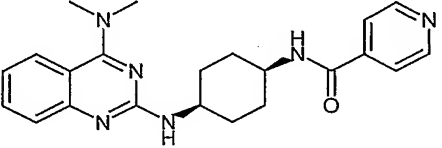
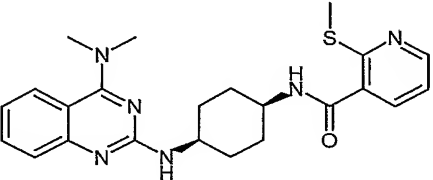
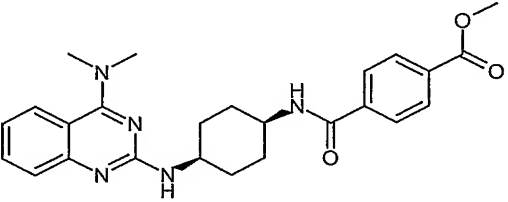
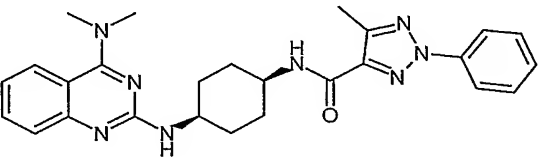
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 292 |  | 547 (M + H) |
| 293 |  | 472 (M + H) |
| 294 |  | 504 (M + H) |
| 295 |  | 504 (M + H) |
| 296 |  | 468 (M + H) |

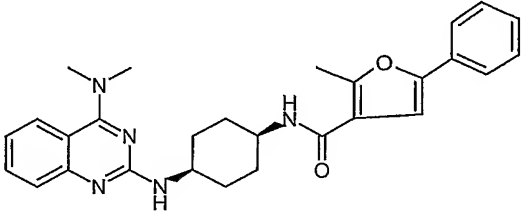
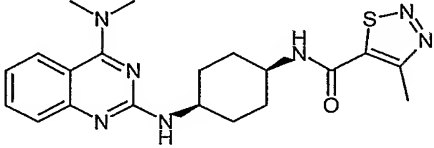
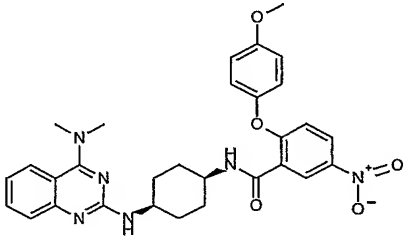
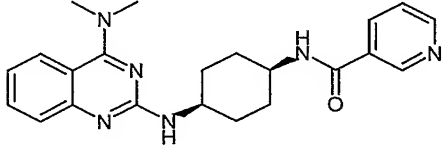
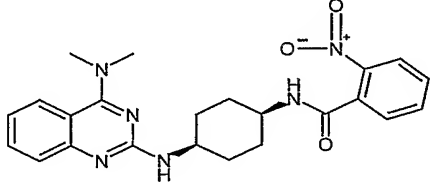
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 297 |  | 538 (M + H) |
| 298 |  | 522 (M + H) |
| 299 |  | 488 (M + H) |
| 300 |  | 590 (M + H) |
| 301 |  | 522 (M + H) |

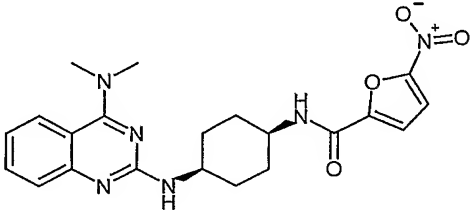
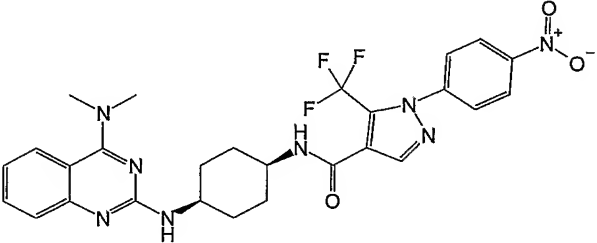
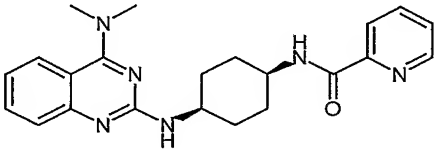
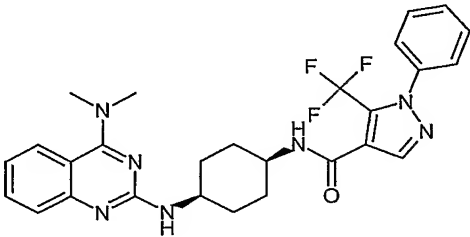
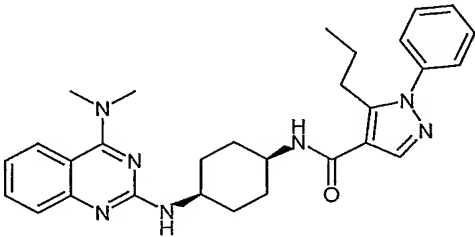
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 302 |  | 520 (M + H) |
| 303 |  | 390 (M + H) |
| 304 |  | 446 (M + H) |
| 305 |  | 468 (M + H) |
| 306 |  | 468 (M + H) |

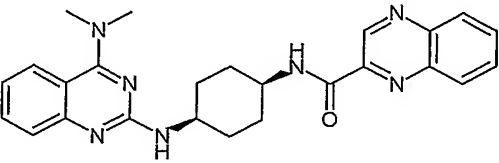
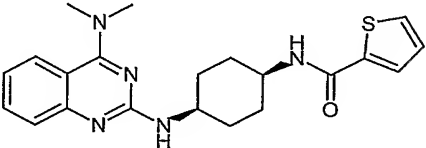
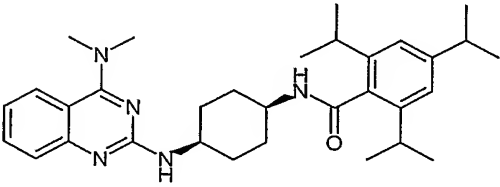
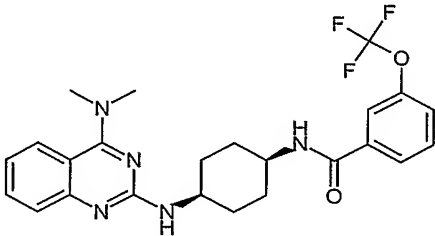
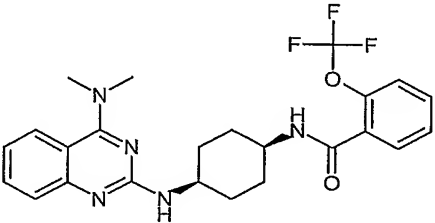
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 307 |  | 432 (M + H) |
| 308 |  | 505 (M + H) |
| 309 |  | 536 (M + H) |
| 310 |  | 469 (M + H) |
| 311 |  | 504 (M + H) |

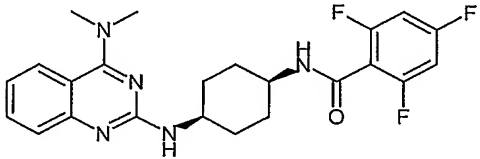
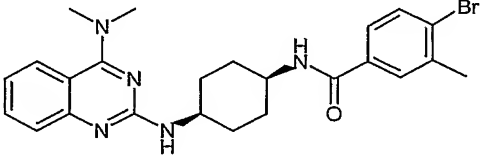
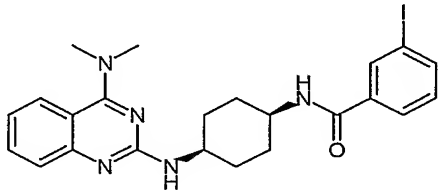
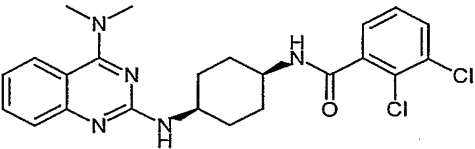
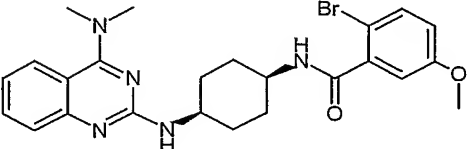
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 312 |  | 430 (M + H) |
| 313 |  | 433 (M + H) |
| 314 |  | 408 (M + H) |
| 315 |  | 451 (M + H) |
| 316 |  | 380 (M + H) |

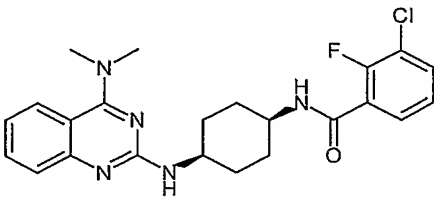
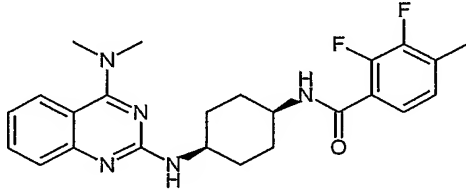
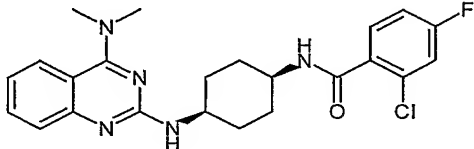
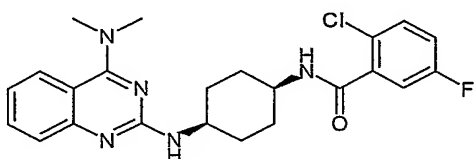
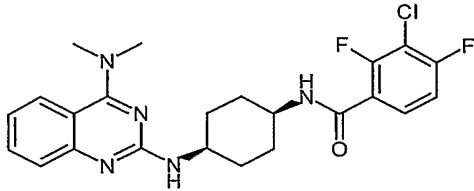
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 317 |  | 476 (M + H) |
| 318 |  | 391 (M + H) |
| 319 |  | 437 (M + H) |
| 320 |  | 448 (M + H) |
| 321 |  | 471 (M + H) |

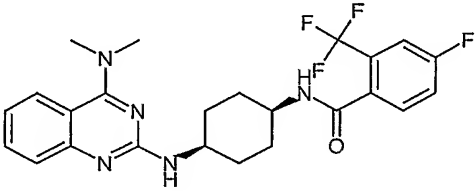
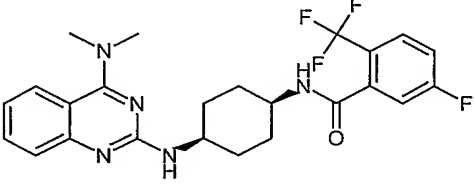
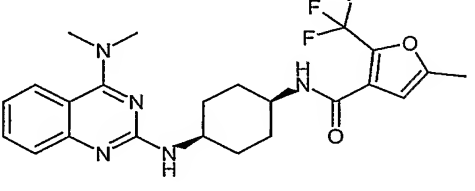
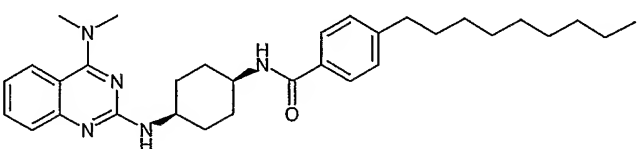
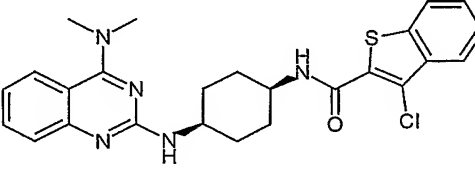
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 322 |  | 470 (M + H) |
| 323 |  | 412 (M + H) |
| 324 |  | 557 (M + H) |
| 325 |  | 391 (M + H) |
| 326 |  | 435 (M + H) |

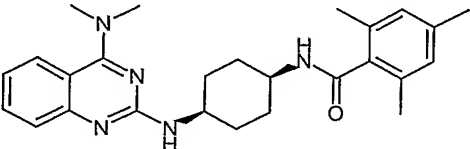
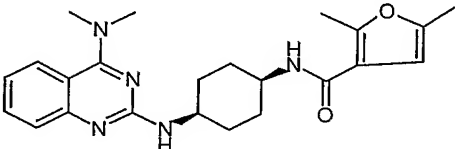
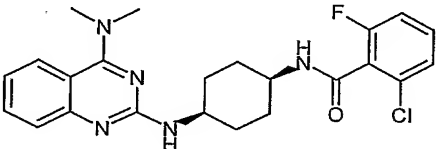
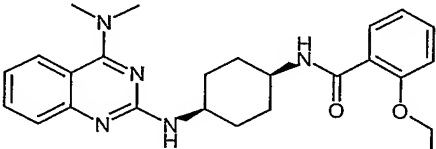
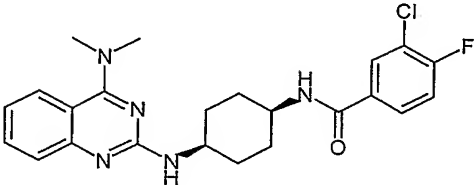
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 327 |  | 425 (M + H) |
| 328 |  | 569 (M + H) |
| 329 |  | 391 (M + H) |
| 330 |  | 524 (M + H) |
| 331 |  | 498 (M + H) |

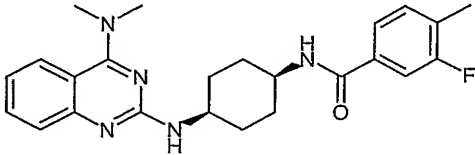
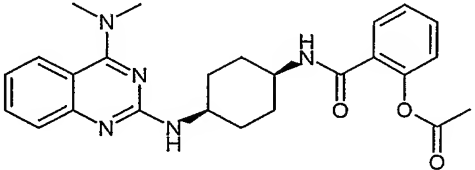
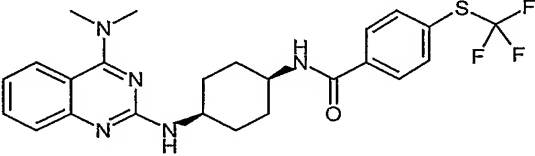
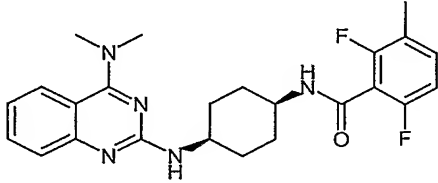
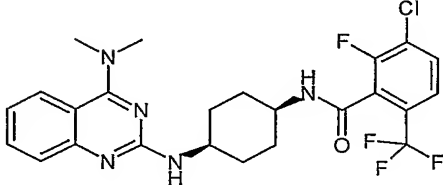
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 332 |  | 442 (M + H) |
| 333 |  | 396 (M + H) |
| 334 |  | 516 (M + H) |
| 335 |  | 474 (M + H) |
| 336 |  | 474 (M + H) |

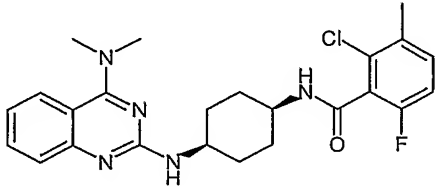
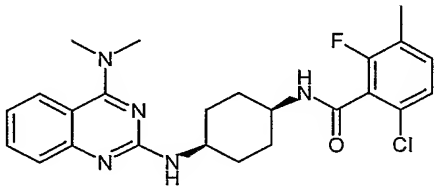
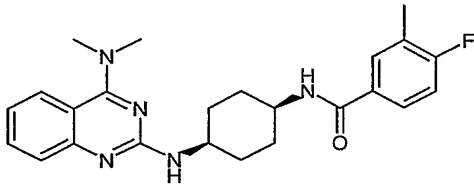
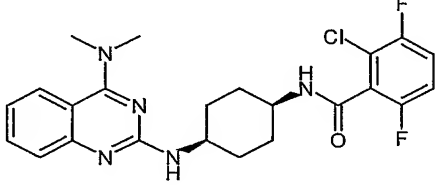
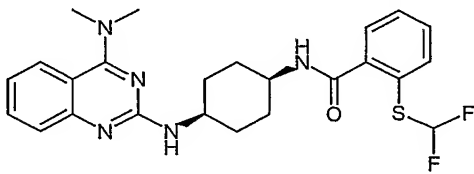
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 337 |  | 444 (M + H) |
| 338 |  | 482 (M + H) |
| 339 |  | 516 (M + H) |
| 340 |  | 458 (M + H) |
| 341 |  | 498 (M + H) |

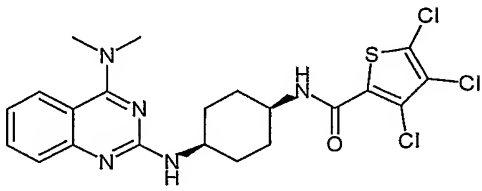
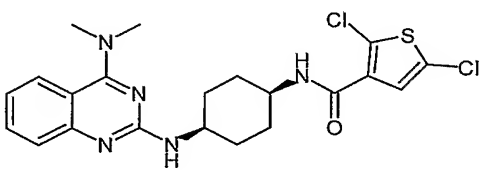
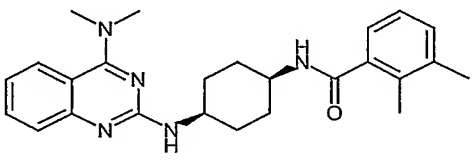
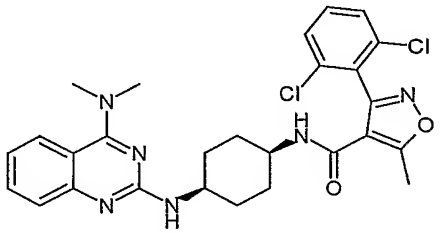
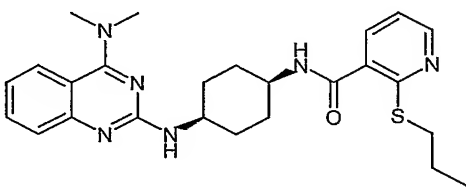
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 342 |  | 442 (M + H) |
| 343 |  | 440 (M + H) |
| 344 |  | 442 (M + H) |
| 345 |  | 442 (M + H) |
| 346 |  | 460 (M + H) |

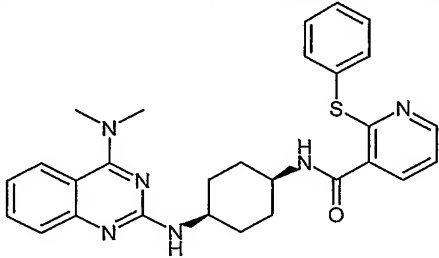
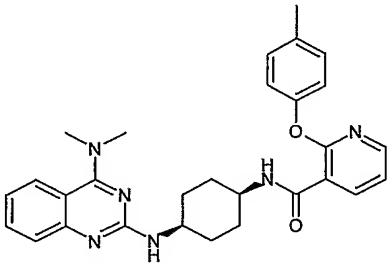
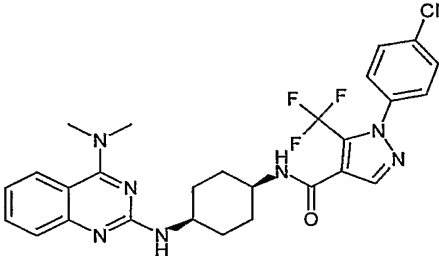
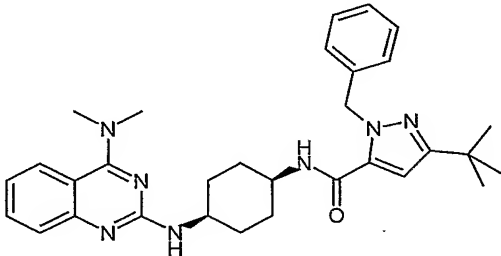
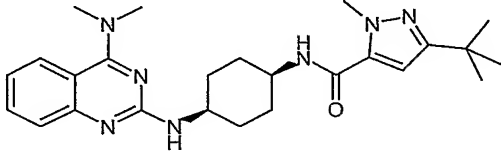
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 347 |  | 476 (M + H) |
| 348 |  | 476 (M + H) |
| 349 |  | 462 (M + H) |
| 350 |  | 516 (M + H) |
| 351 |  | 480 (M + H) |

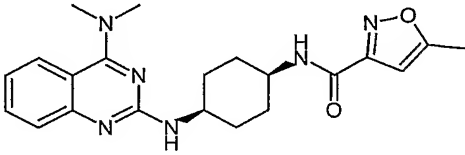
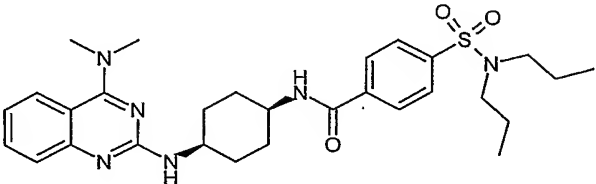
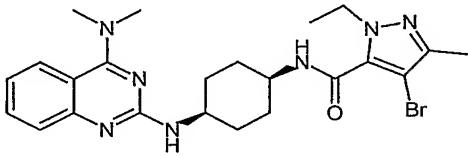
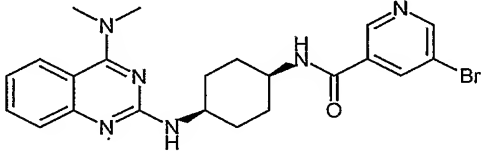
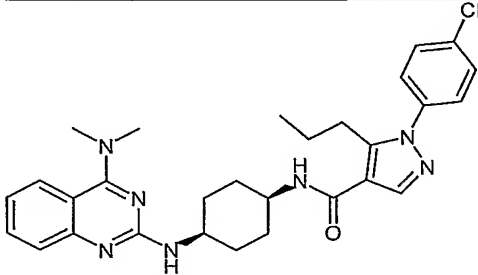
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 352 |  | 432 (M + H) |
| 353 |  | 408 (M + H) |
| 354 |  | 442 (M + H) |
| 355 |  | 434 (M + H) |
| 356 |  | 442 (M + H) |

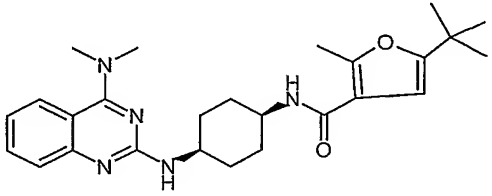
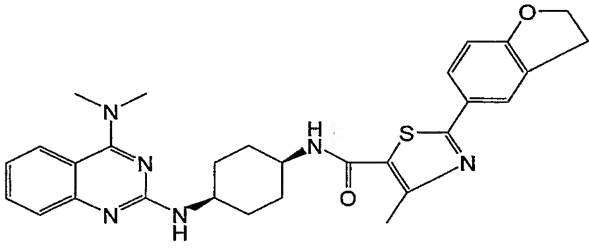
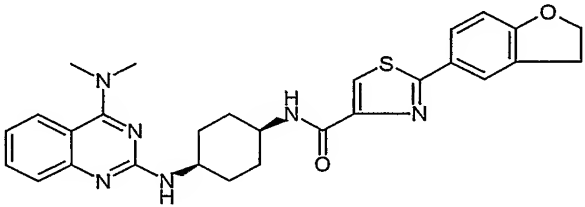
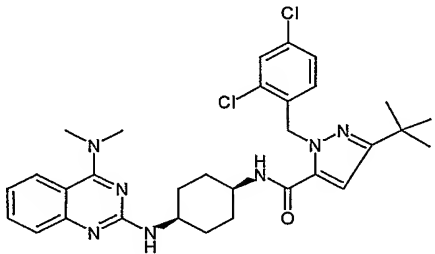
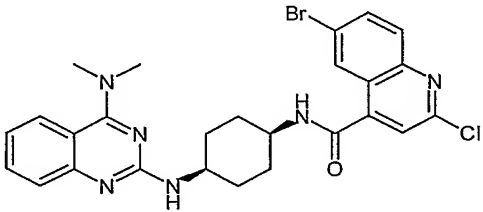
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 357 |  | 422 (M + H) |
| 358 |  | 406 (M + H) |
| 359 |  | 490 (M + H) |
| 360 |  | 440 (M + H) |
| 361 |  | 510 (M + H) |

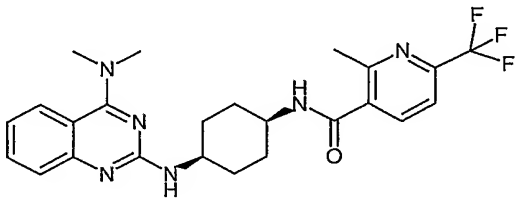
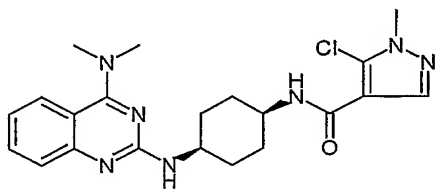
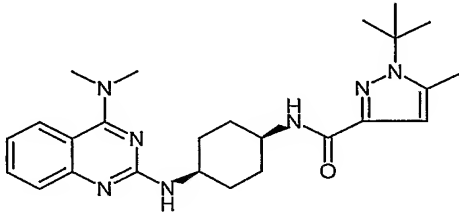
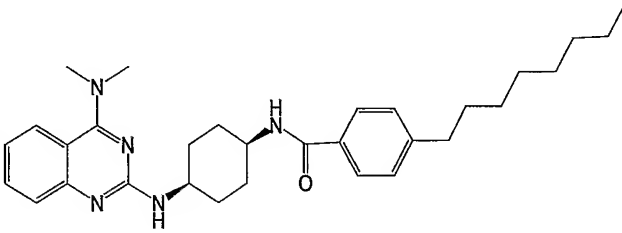
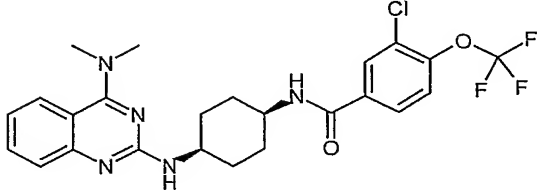
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 362 |  | 456 (M + H) |
| 363 |  | 456 (M + H) |
| 364 |  | 422 (M + H) |
| 365 |  | 460 (M + H) |
| 366 |  | 472 (M + H) |

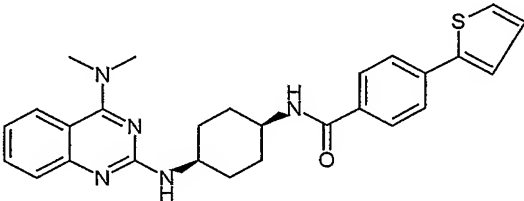
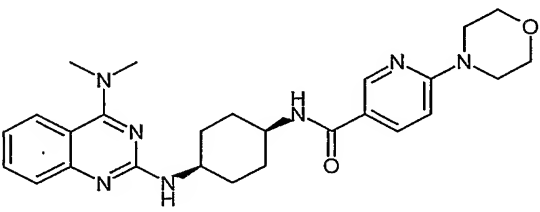
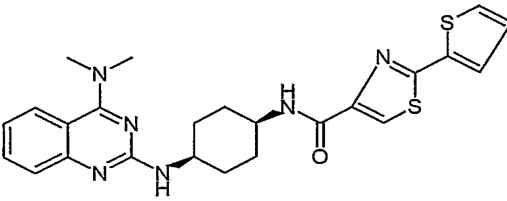
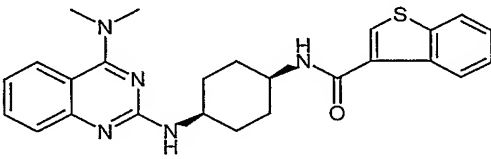
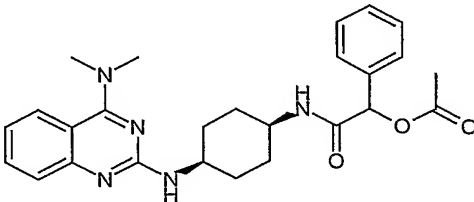
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 367 |  | 498 (M + H) |
| 368 |  | 464 (M + H) |
| 369 |  | 418 (M + H) |
| 370 |  | 539 (M + H) |
| 371 |  | 465 (M + H) |

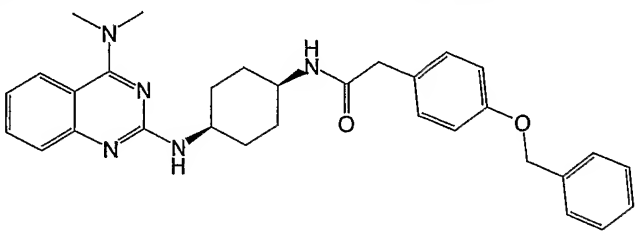
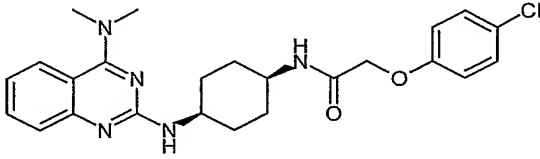
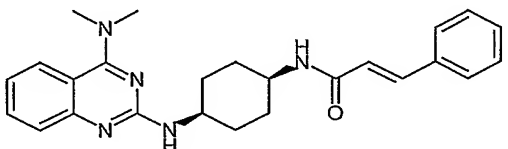
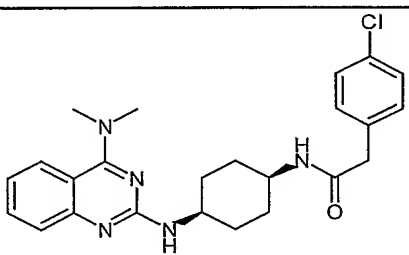
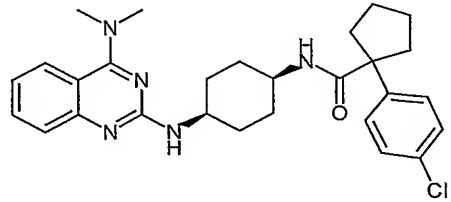
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 372 |  | 499 (M + H) |
| 373 |  | 497 (M + H) |
| 374 |  | 558 (M + H) |
| 375 |  | 526 (M + H) |
| 376 |  | 450 (M + H) |

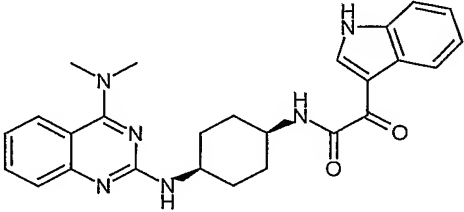
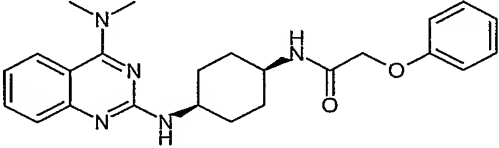
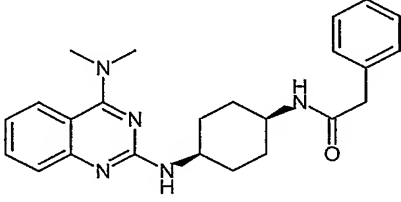
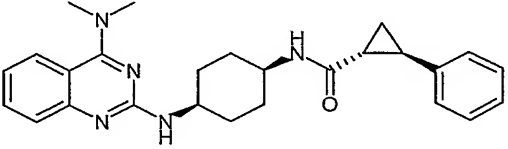
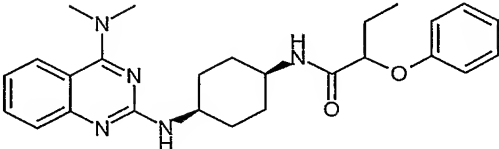
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 377 |  | 395 (M + H) |
| 378 |  | 553 (M + H) |
| 379 |  | 500 (M + H) |
| 380 |  | 469 (M + H) |
| 381 |  | 532 (M + H) |

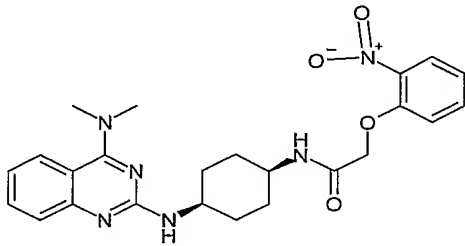
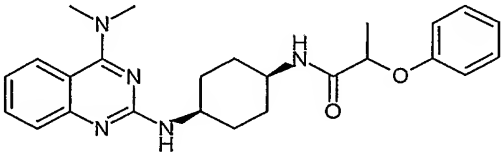
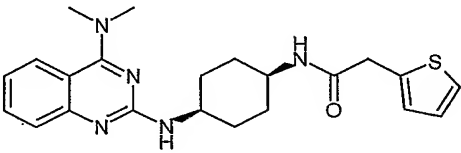
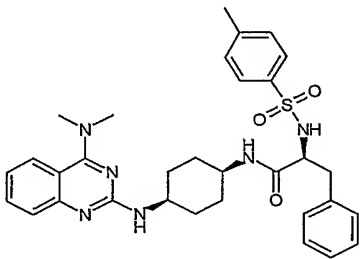
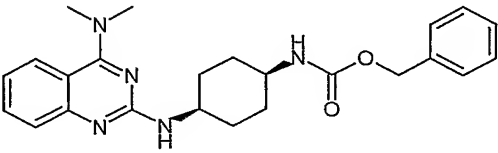
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 382 |  | 450 (M + H) |
| 383 |  | 529 (M + H) |
| 384 |  | 515 (M + H) |
| 385 |  | 594 (M + H) |
| 386 |  | 553 (M + H) |

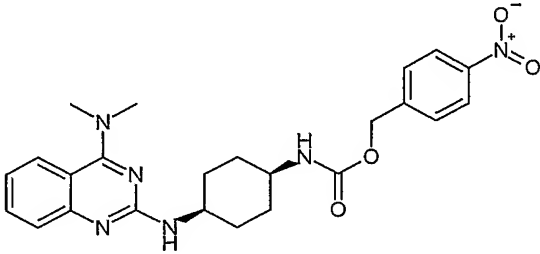
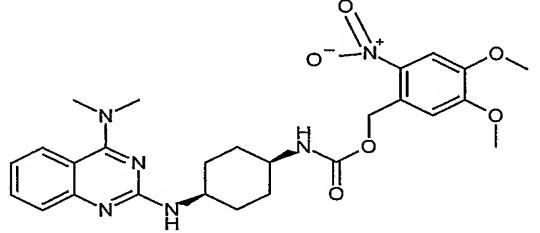
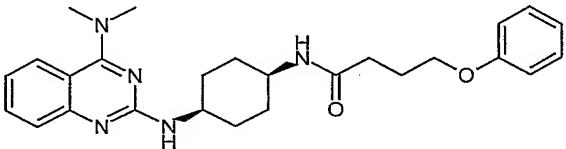
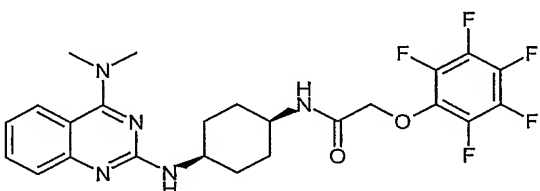
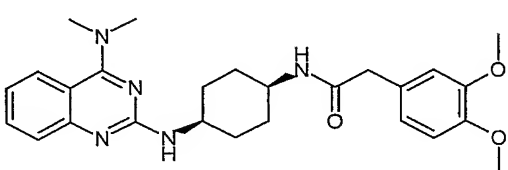
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 387 |  | 473 (M + H) |
| 388 |  | 428 (M + H) |
| 389 |  | 450 (M + H) |
| 390 |  | 502 (M + H) |
| 391 |  | 508 (M + H) |

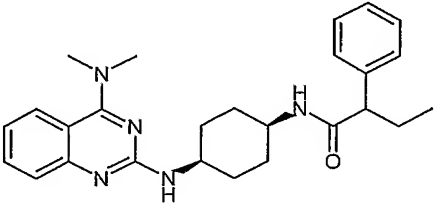
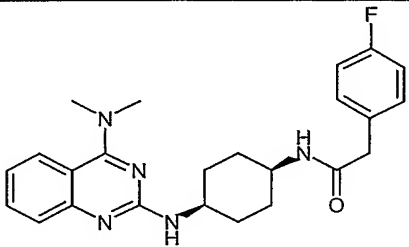
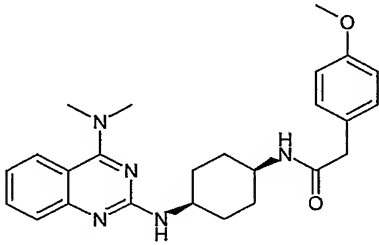
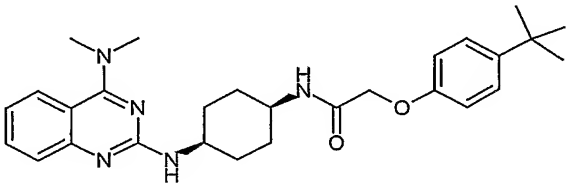
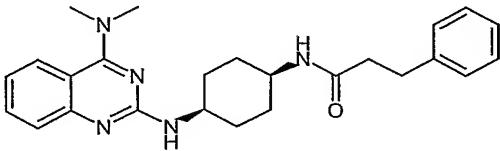
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 392 |  | 472 (M + H) |
| 393 |  | 476 (M + H) |
| 394 |  | 479 (M + H) |
| 395 |  | 446 (M + H) |
| 396 |  | 462 (M + H) |

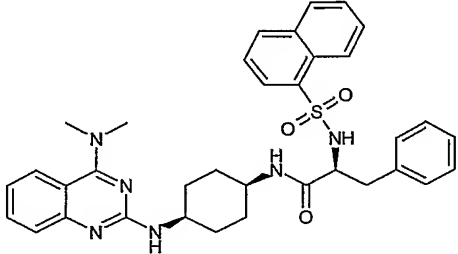
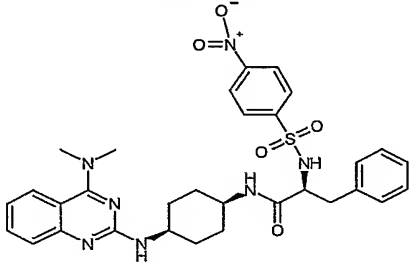
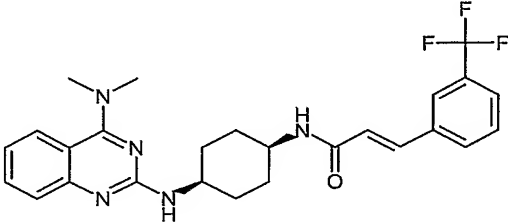
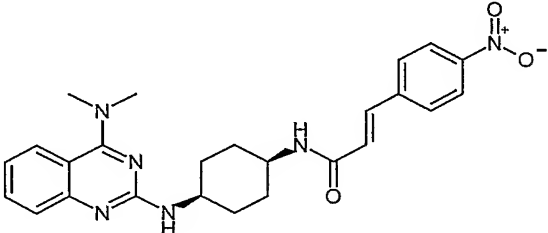
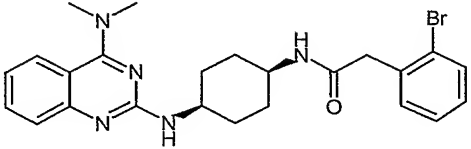
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 397 |  | 510 (M + H) |
| 398 |  | 454 (M + H) |
| 399 |  | 416 (M + H) |
| 400 |  | 438 (M + H) |
| 401 |  | 492 (M + H) |

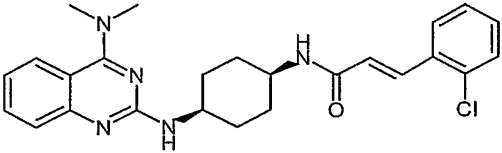
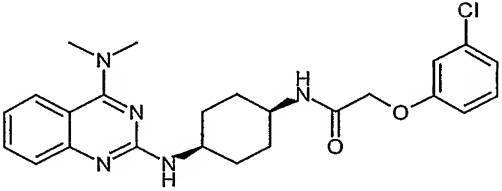
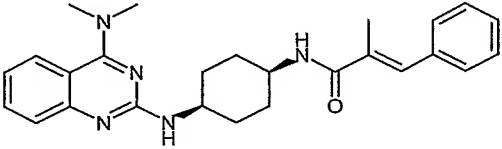
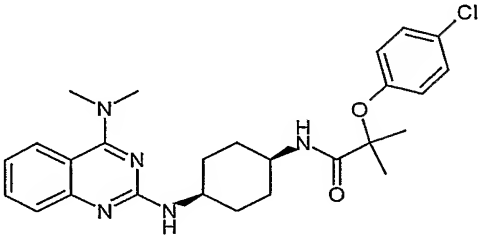
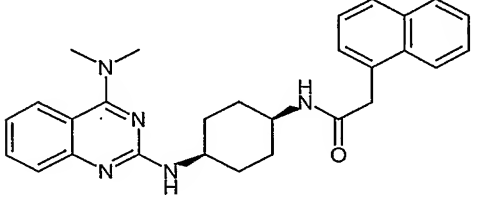
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 402 |  | 457 (M + H) |
| 403 |  | 420 (M + H) |
| 404 |  | 404 (M + H) |
| 405 |  | 430 (M + H) |
| 406 |  | 448 (M + H) |

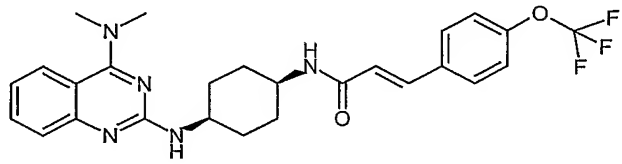
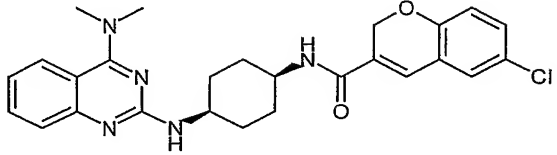
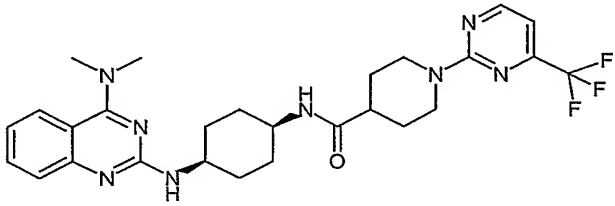
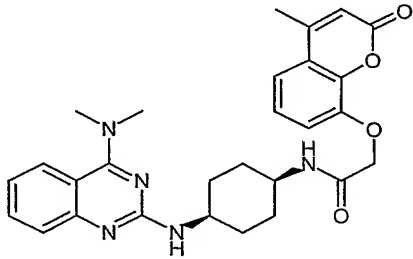
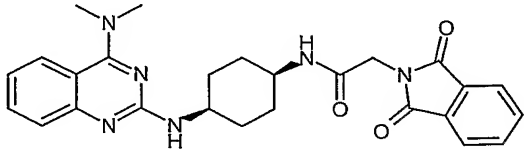
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 407 |  | 465 (M + H) |
| 408 |  | 434 (M + H) |
| 409 |  | 410 (M + H) |
| 410 |  | 587 (M + H) |
| 411 |  | 420 (M + H) |

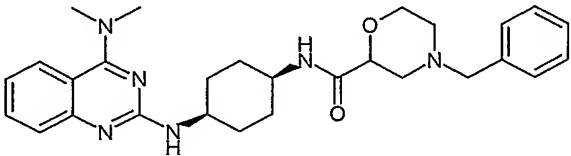
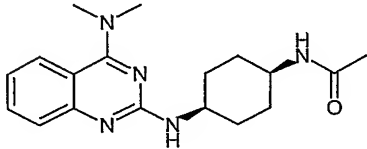
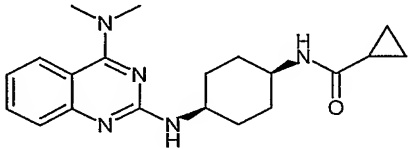
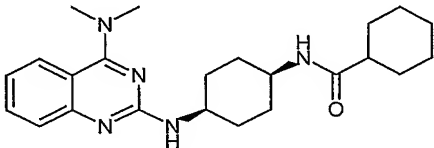
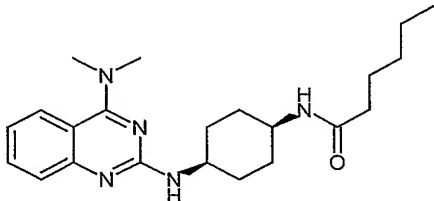
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 412 |  | 465 (M + H) |
| 413 |  | 525 (M + H) |
| 414 |  | 448 (M + H) |
| 415 |  | 510 (M + H) |
| 416 |  | 464 (M + H) |

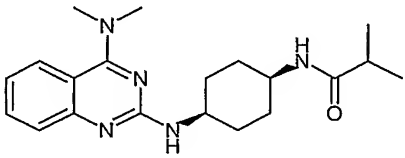
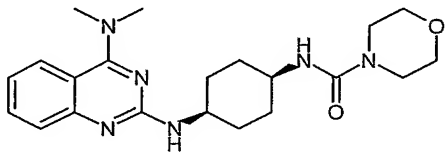
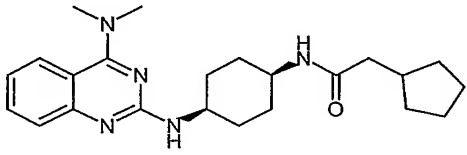
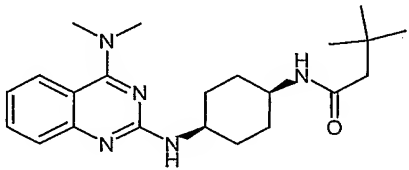
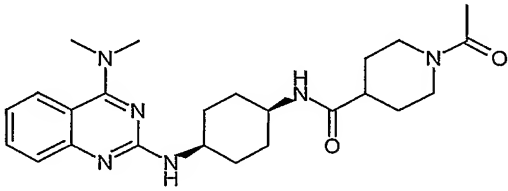
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 417 |  | 432 (M + H) |
| 418 |  | 422 (M + H) |
| 419 |  | 434 (M + H) |
| 420 |  | 476 (M + H) |
| 421 |  | 418 (M + H) |

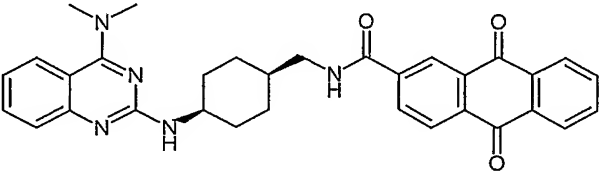
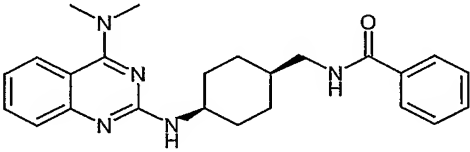
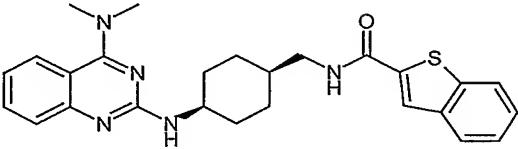
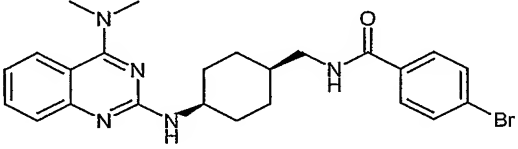
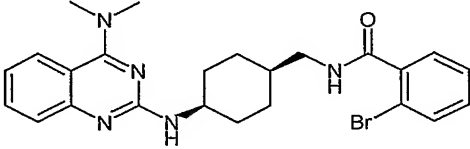
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 422 |  | 623 (M + H) |
| 423 |  | 618 (M + H) |
| 424 |  | 484 (M + H) |
| 425 |  | 461 (M + H) |
| 426 |  | 482 (M + H) |

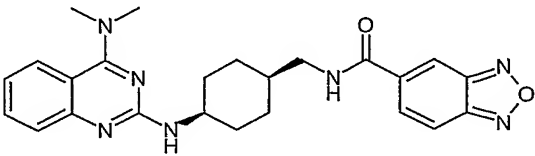
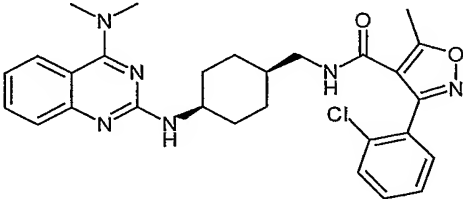
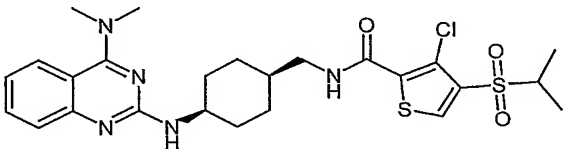
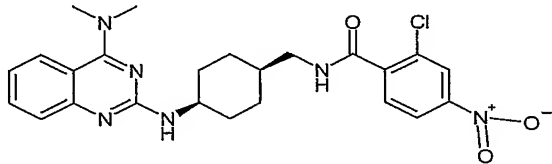
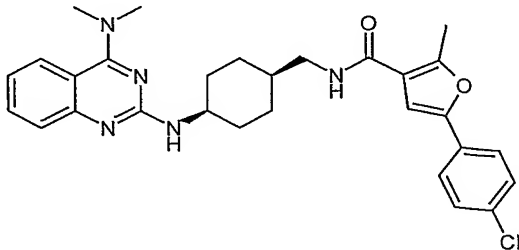
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 427 |  | 450 (M + H) |
| 428 |  | 454 (M + H) |
| 429 |  | 430 (M + H) |
| 430 |  | 482 (M + H) |
| 431 |  | 454 (M + H) |

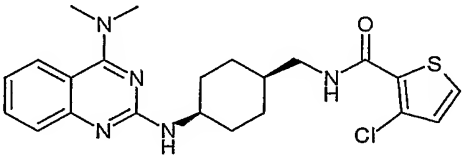
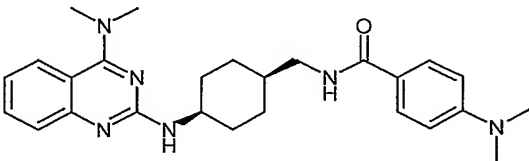
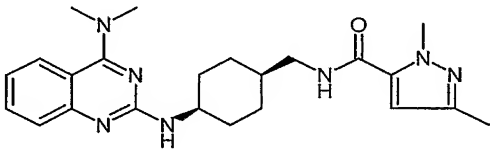
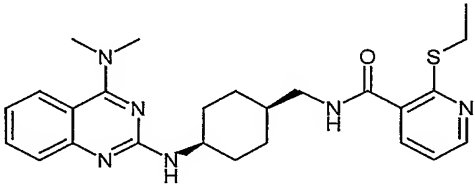
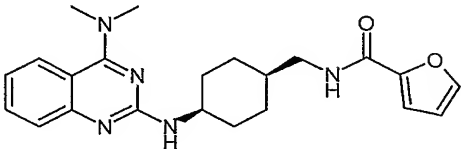
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 432 |  | 500 (M + H) |
| 433 |  | 478 (M + H) |
| 434 |  | 543 (M + H) |
| 435 |  | 502 (M + H) |
| 436 |  | 473 (M + H) |

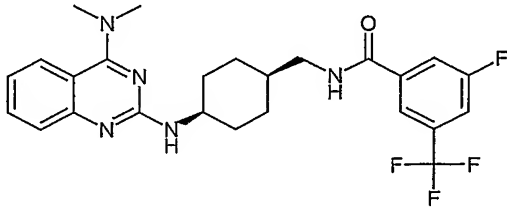
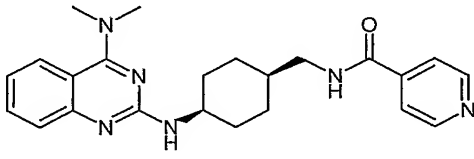
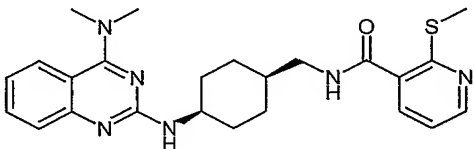
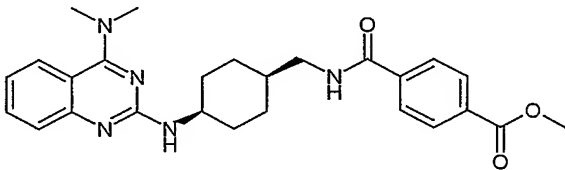
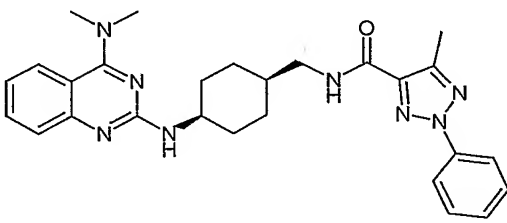
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 437 |  | 489 (M + H) |
| 438 |  | 328 (M + H) |
| 439 |  | 354 (M + H) |
| 440 |  | 396 (M + H) |
| 441 |  | 384 (M + H) |

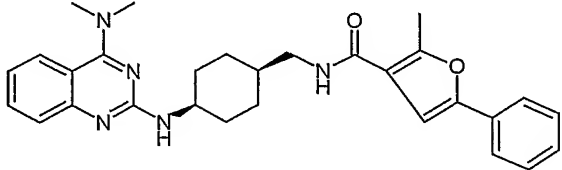
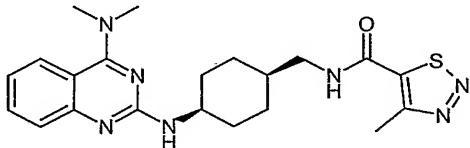
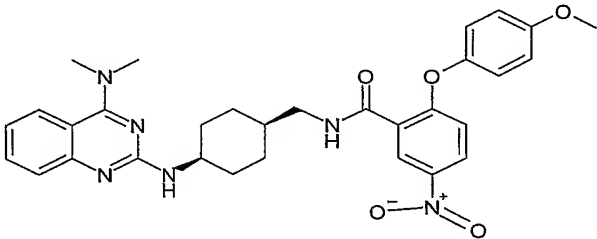
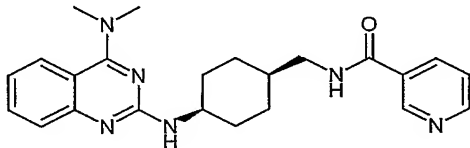
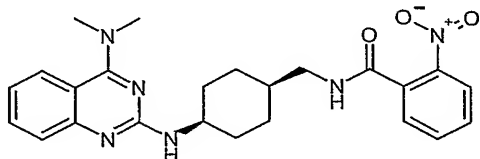
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 442 |  | 356 (M + H) |
| 443 |  | 399 (M + H) |
| 444 |  | 396 (M + H) |
| 445 |  | 384 (M + H) |
| 446 |  | 439 (M + H) |

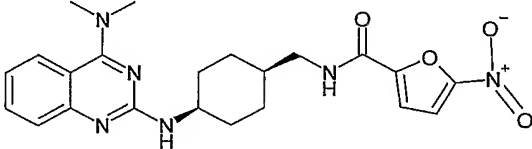
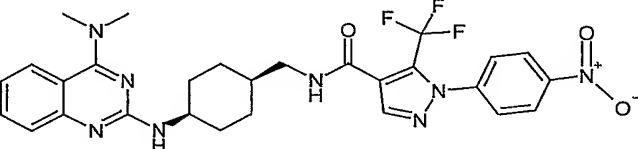
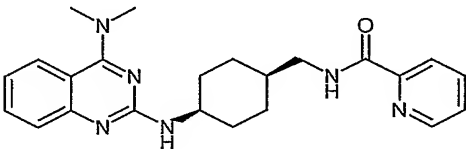
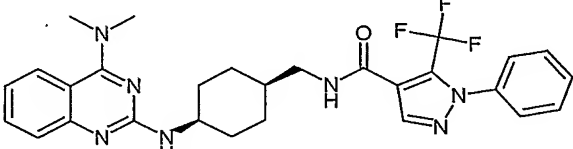
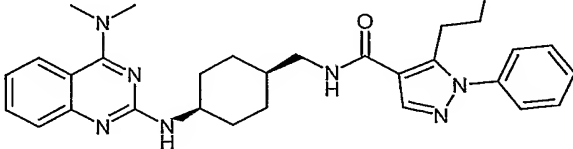
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 447 |  | 534 (M + H) |
| 448 |  | 404 (M + H) |
| 449 |  | 460 (M + H) |
| 450 |  | 482 (M + H) |
| 451 |  | 482 (M + H) |

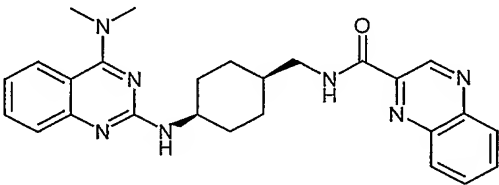
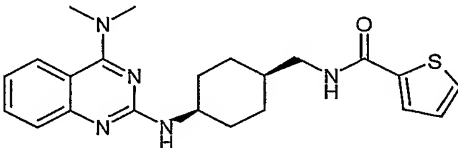
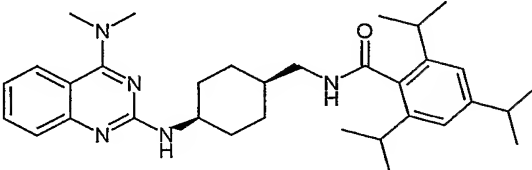
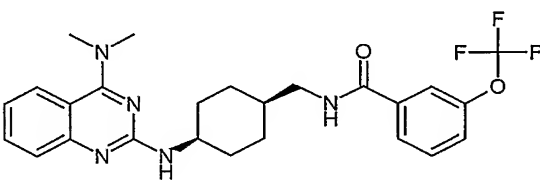
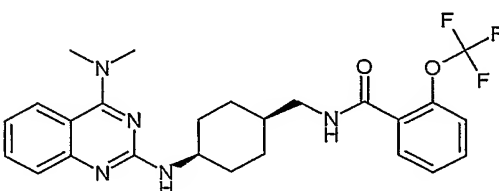
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 452 |  | 446 (M + H) |
| 453 |  | 519 (M + H) |
| 454 |  | 550 (M + H) |
| 455 |  | 483 (M + H) |
| 456 |  | 518 (M + H) |

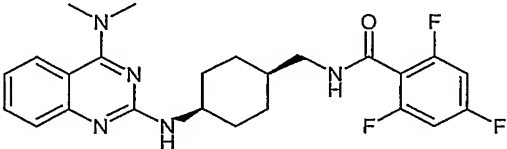
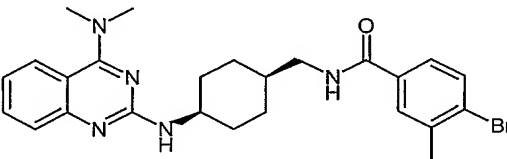
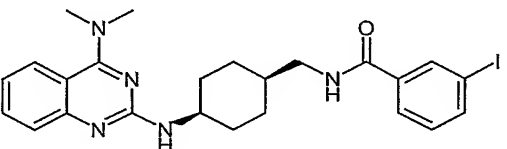
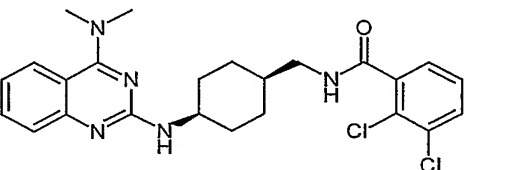
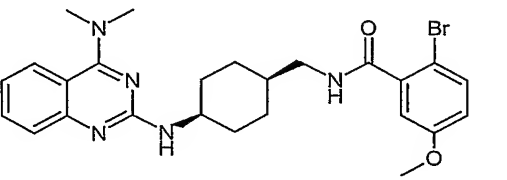
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 457 |  | 444 (M + H) |
| 458 |  | 447 (M + H) |
| 459 |  | 422 (M + H) |
| 460 |  | 465 (M + H) |
| 461 |  | 394 (M + H) |

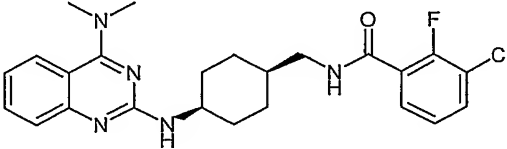
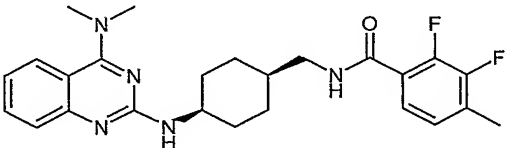
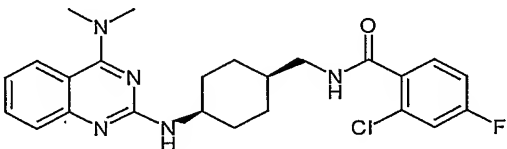
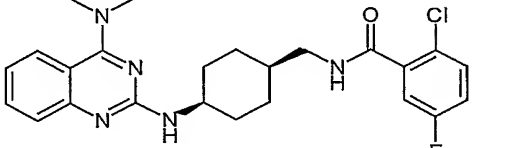
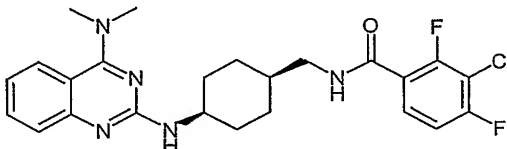
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 462 |  | 490 (M + H) |
| 463 |  | 405 (M + H) |
| 464 |  | 451 (M + H) |
| 465 |  | 462 (M + H) |
| 466 |  | 485 (M + H) |

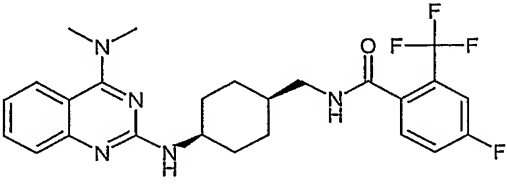
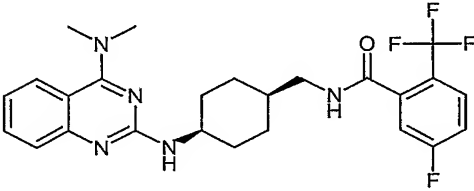
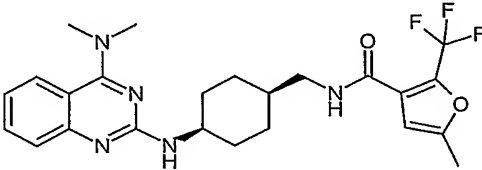
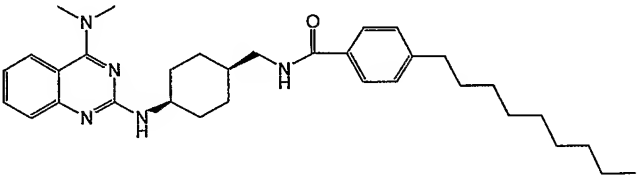
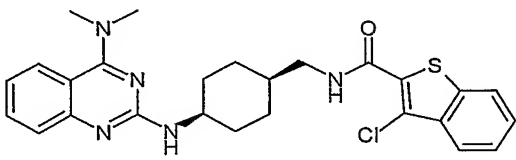
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 467 |  | 484 (M + H) |
| 468 |  | 426 (M + H) |
| 469 |  | 571 (M + H) |
| 470 |  | 405 (M + H) |
| 471 |  | 449 (M + H) |

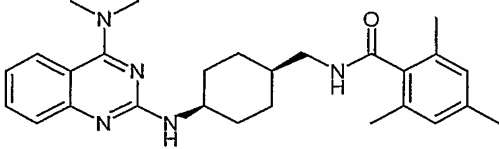
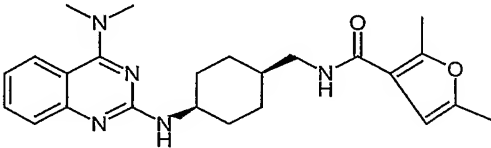
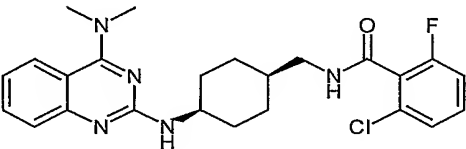
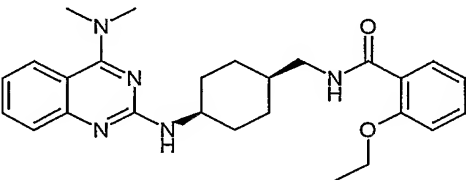
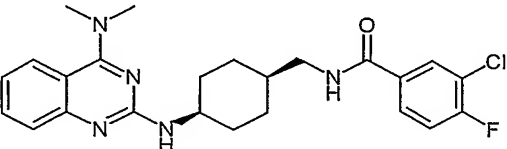
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 472 |  | 439 (M + H) |
| 473 |  | 583 (M + H) |
| 474 |  | 405 (M + H) |
| 475 |  | 538 (M + H) |
| 476 |  | 512 (M + H) |

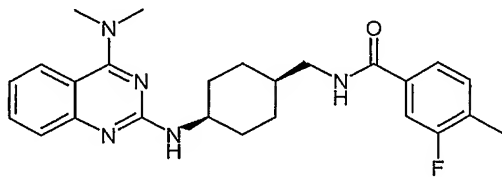
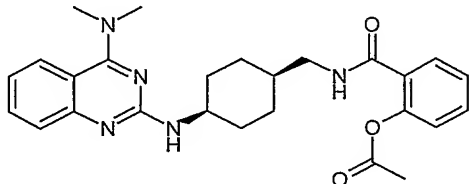
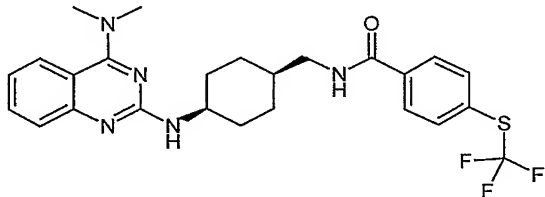
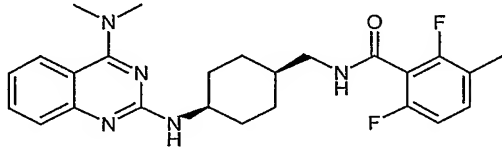
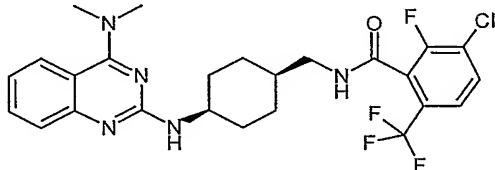
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 477 |  | 456 (M + H) |
| 478 |  | 410 (M + H) |
| 479 |  | 530 (M + H) |
| 480 |  | 488 (M + H) |
| 481 |  | 488 (M + H) |

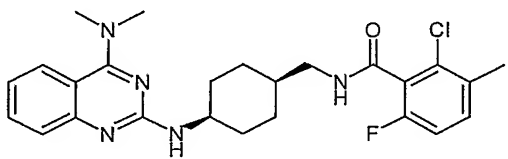
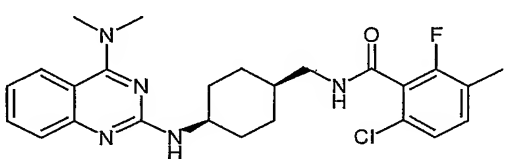
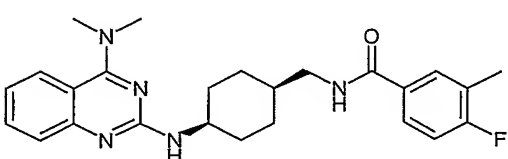
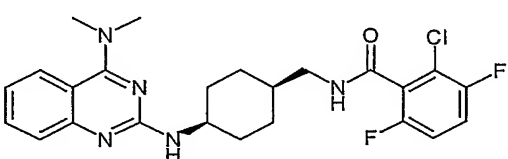
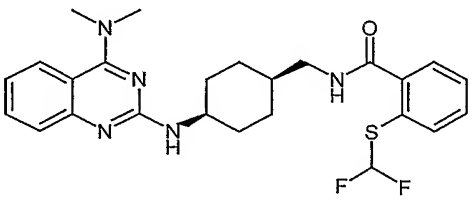
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 482 |  | 458 (M + H) |
| 483 |  | 496 (M + H) |
| 484 |  | 530 (M + H) |
| 485 |  | 472 (M + H) |
| 486 |  | 512 (M + H) |

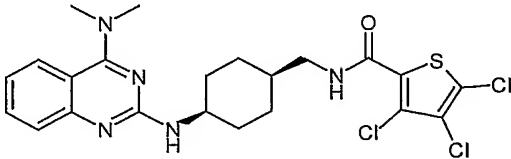
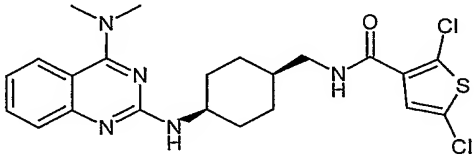
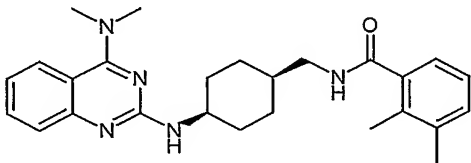
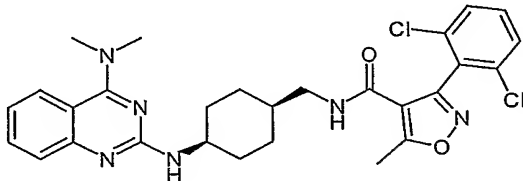
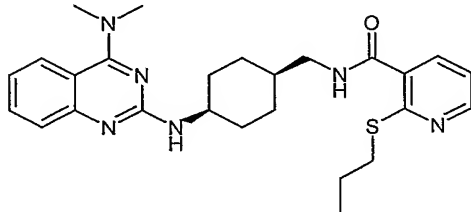
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 487 |  | 456 (M + H) |
| 488 |  | 454 (M + H) |
| 489 |  | 456 (M + H) |
| 490 |  | 456 (M + H) |
| 491 |  | 474 (M + H) |

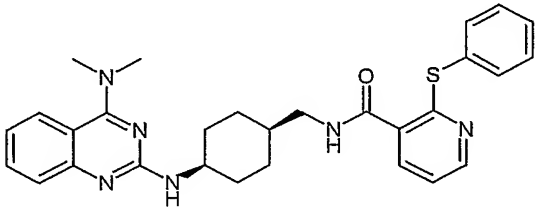
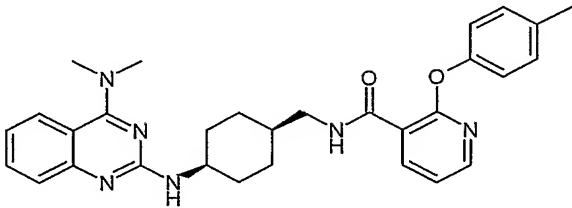
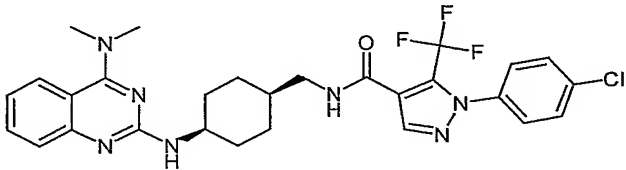
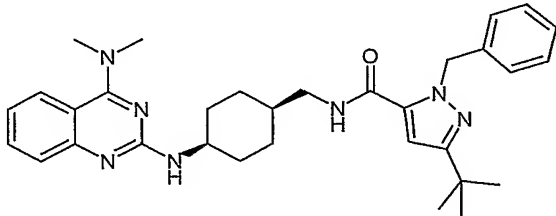
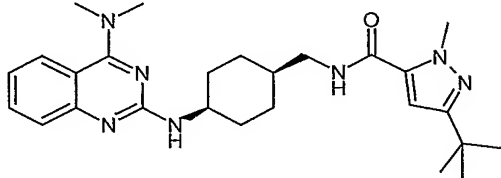
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 492 |  | 490 (M + H) |
| 493 |  | 490 (M + H) |
| 494 |  | 476 (M + H) |
| 495 |  | 530 (M + H) |
| 496 |  | 494 (M + H) |

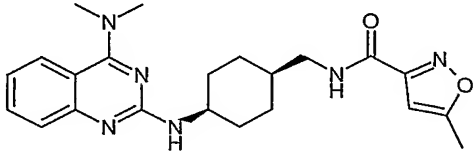
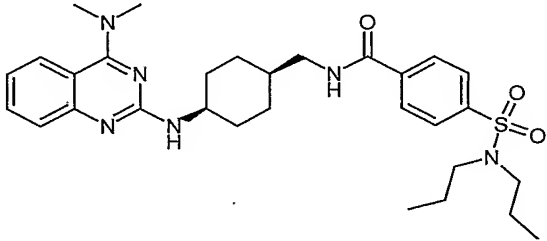
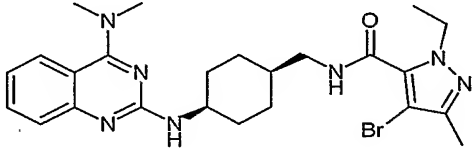
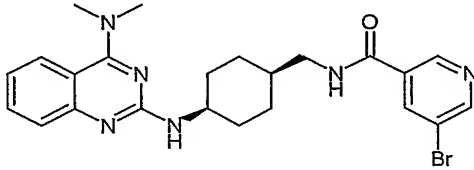
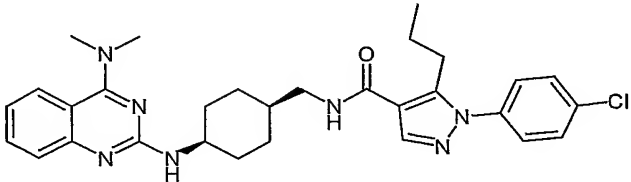
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 497 |  | 446 (M + H) |
| 498 |  | 422 (M + H) |
| 499 |  | 456 (M + H) |
| 500 |  | 448 (M + H) |
| 501 |  | 456 (M + H) |

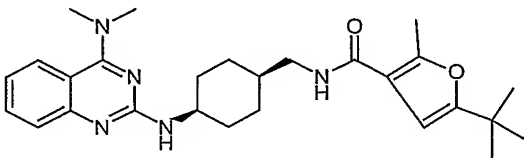
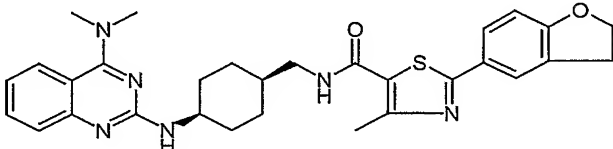
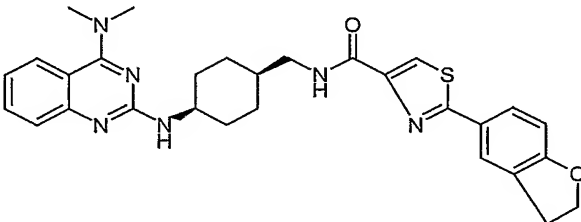
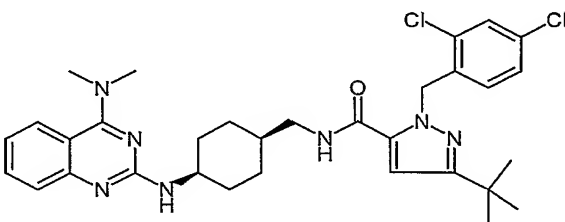
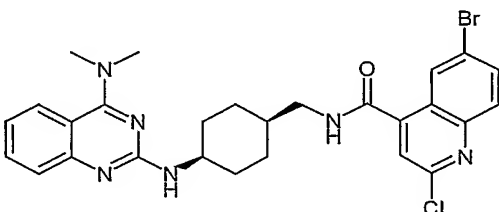
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 502 |  | 436 (M + H) |
| 503 |  | 420 (M + H) |
| 504 |  | 504 (M + H) |
| 505 |  | 454 (M + H) |
| 506 |  | 524 (M + H) |

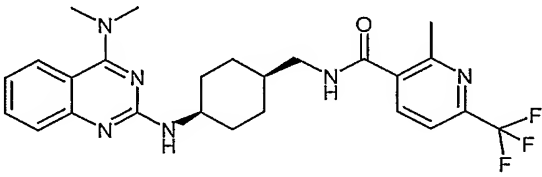
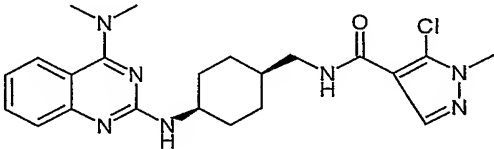
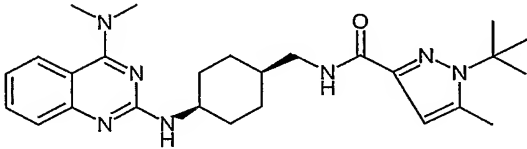
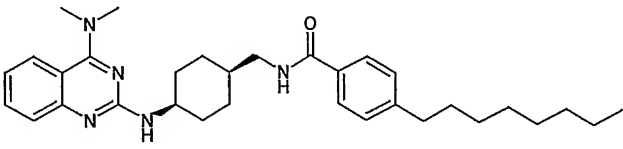
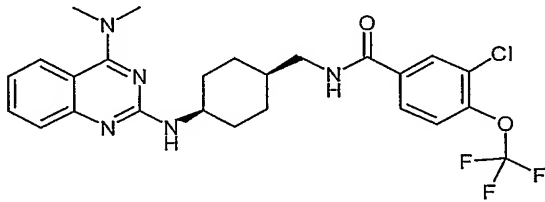
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 507 |  | 470 (M + H) |
| 508 |  | 470 (M + H) |
| 509 |  | 436 (M + H) |
| 510 |  | 474 (M + H) |
| 511 |  | 486 (M + H) |

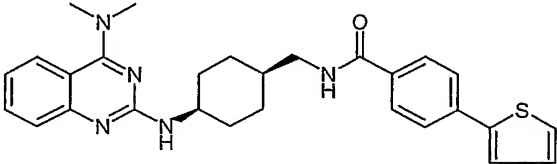
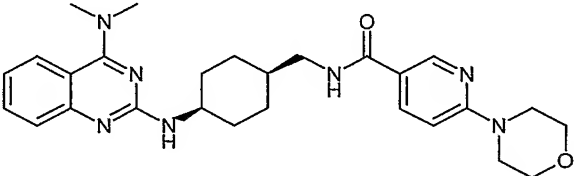
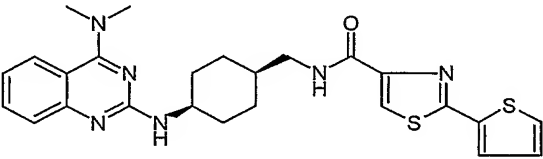
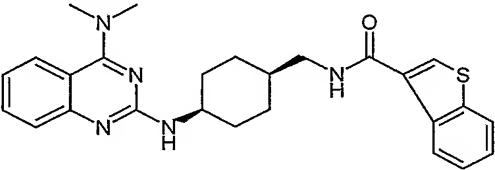
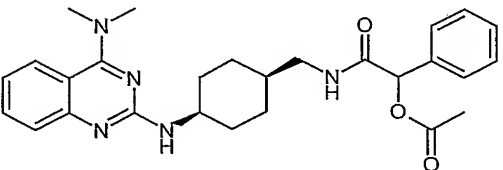
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 512 |  | 512 (M + H) |
| 513 |  | 478 (M + H) |
| 514 |  | 432 (M + H) |
| 515 |  | 553 (M + H) |
| 516 |  | 479 (M + H) |

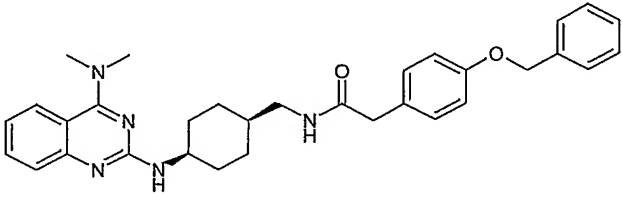
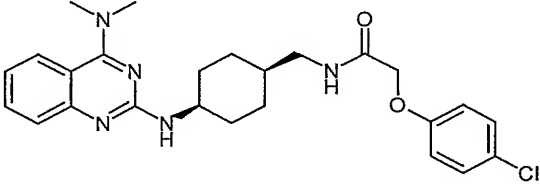
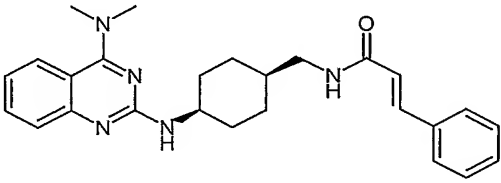
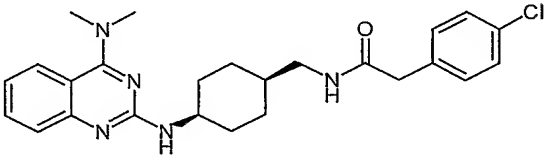
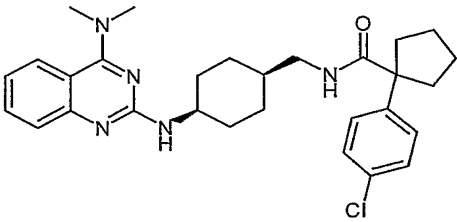
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 517 |  | 513 (M + H) |
| 518 |  | 511 (M + H) |
| 519 |  | 572 (M + H) |
| 520 |  | 540 (M + H) |
| 521 |  | 464 (M + H) |

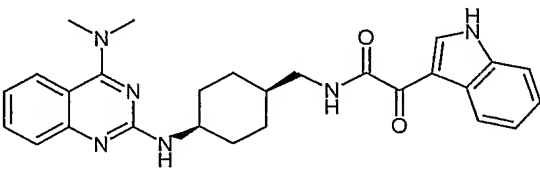
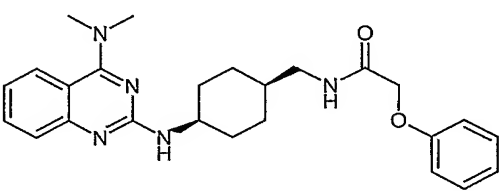
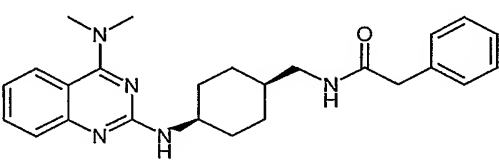
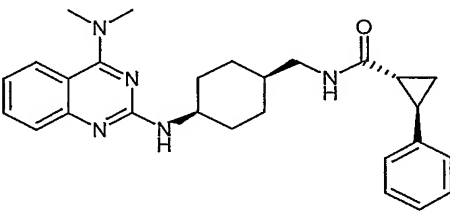
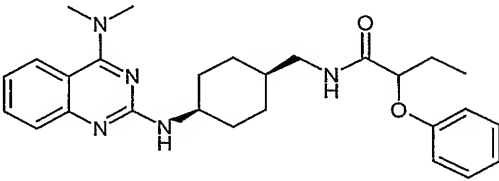
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 522 |  | 409 (M + H) |
| 523 |  | 567 (M + H) |
| 524 |  | 514 (M + H) |
| 525 |  | 483 (M + H) |
| 526 |  | 546 (M + H) |

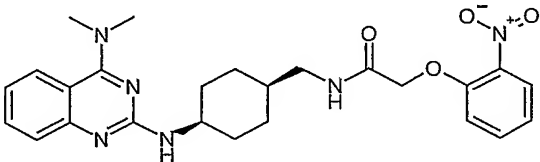
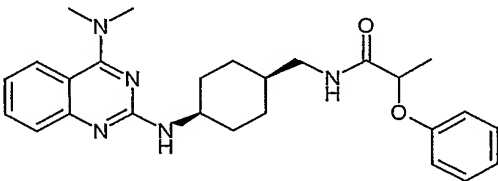
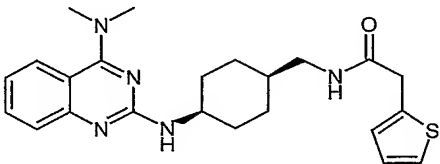
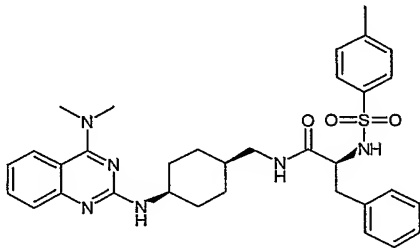
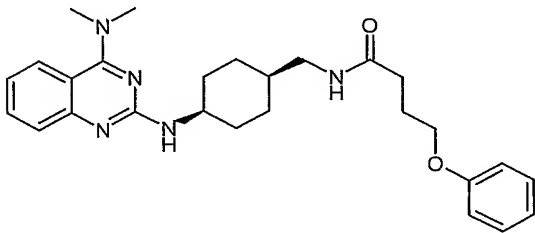
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 527 |  | 464 (M + H) |
| 528 |  | 543 (M + H) |
| 529 |  | 529 (M + H) |
| 530 |  | 608 (M + H) |
| 531 |  | 567 (M + H) |

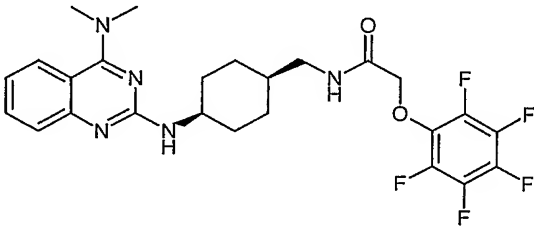
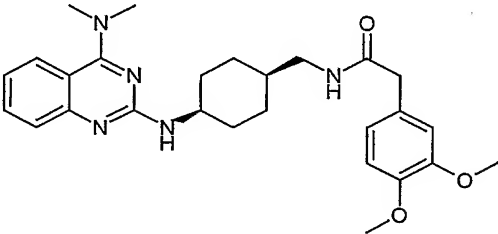
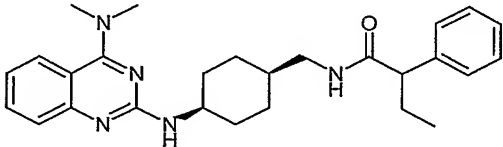
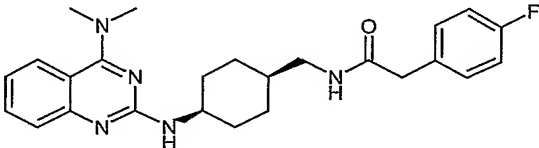
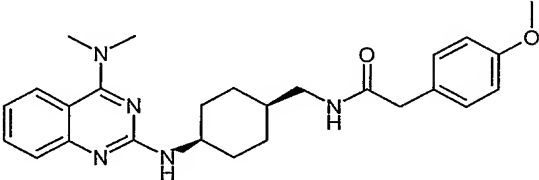
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 532 |  | 487 (M + H) |
| 533 |  | 442 (M + H) |
| 534 |  | 464 (M + H) |
| 535 |  | 516 (M + H) |
| 536 |  | 522 (M + H) |

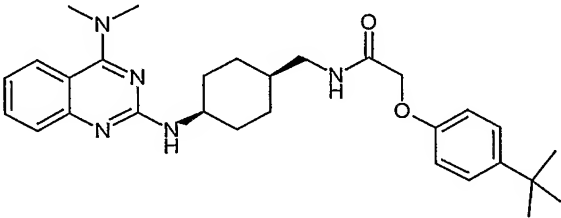
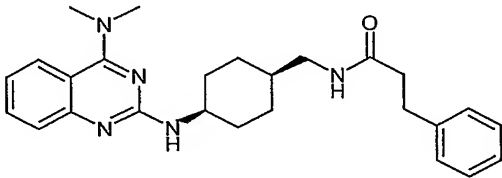
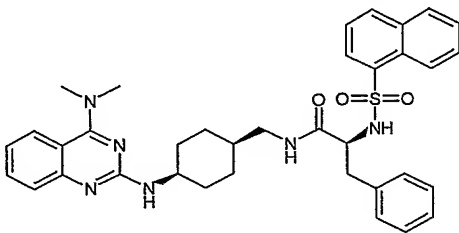
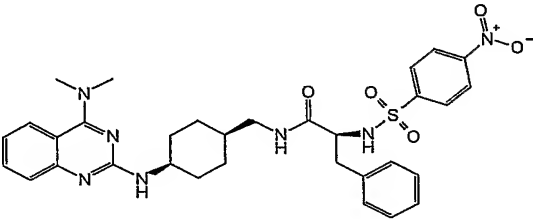
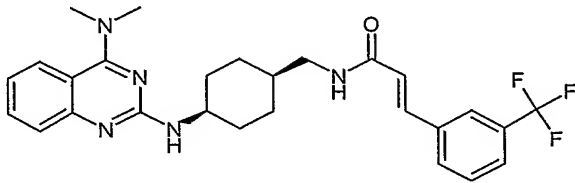
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 537 |  | 486 (M + H) |
| 538 |  | 490 (M + H) |
| 539 |  | 493 (M + H) |
| 540 |  | 460 (M + H) |
| 541 |  | 476 (M + H) |

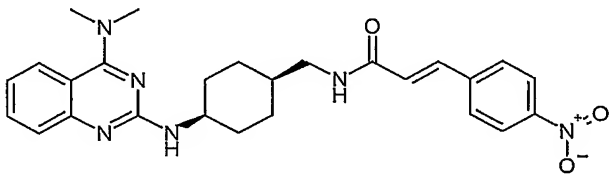
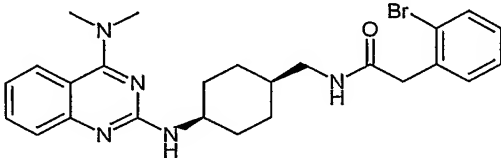
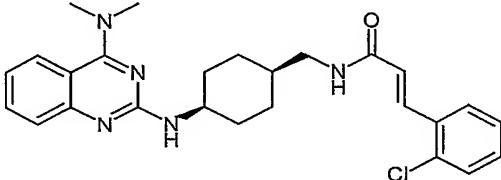
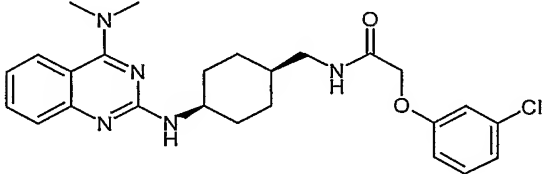
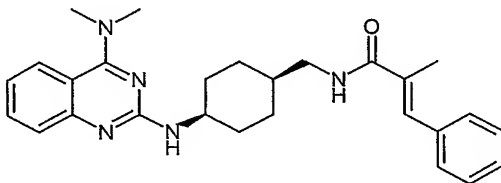
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 542 |  | 524 (M + H) |
| 543 |  | 468 (M + H) |
| 544 |  | 430 (M + H) |
| 545 |  | 452 (M + H) |
| 546 |  | 506 (M + H) |

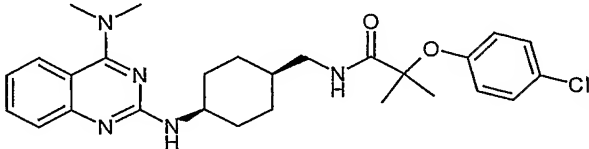
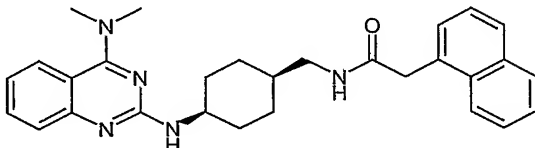
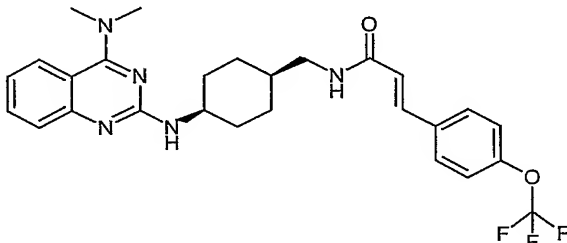
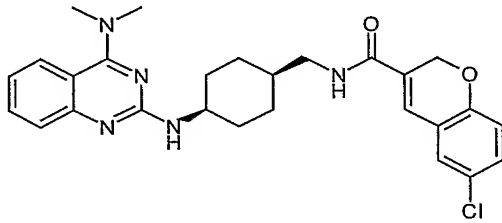
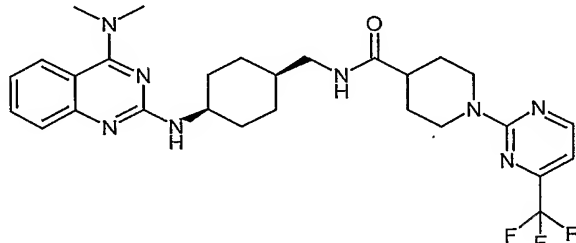
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 547 |  | 471 (M + H) |
| 548 |  | 434 (M + H) |
| 549 |  | 418 (M + H) |
| 550 |  | 444 (M + H) |
| 551 |  | 462 (M + H) |

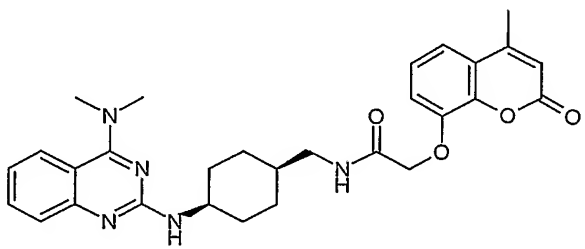
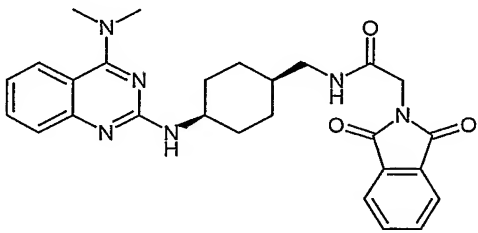
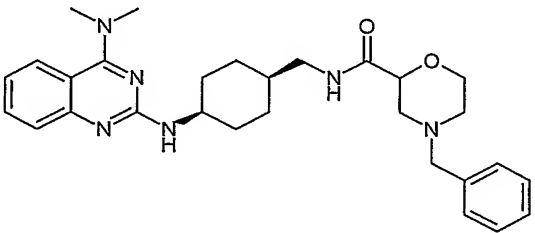
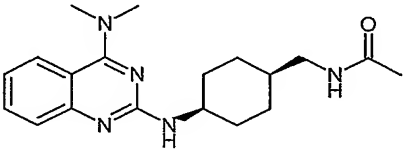
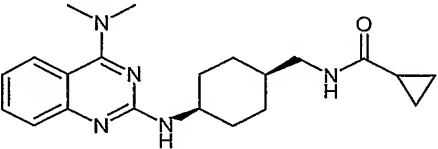
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 552 |  | 479 (M + H) |
| 553 |  | 448 (M + H) |
| 554 |  | 424 (M + H) |
| 555 |  | 601 (M + H) |
| 556 |  | 462 (M + H) |

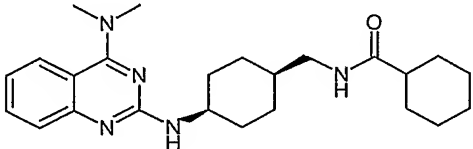
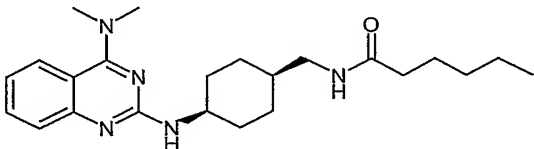
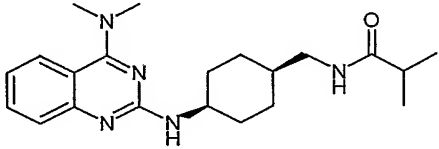
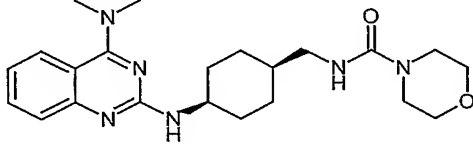
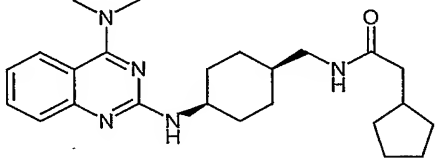
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 557 |  | 524 (M + H) |
| 558 |  | 478 (M + H) |
| 559 |  | 446 (M + H) |
| 560 |  | 436 (M + H) |
| 561 |  | 448 (M + H) |

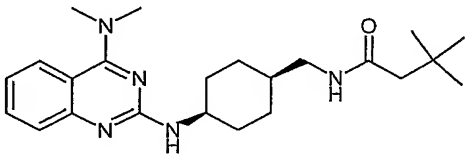
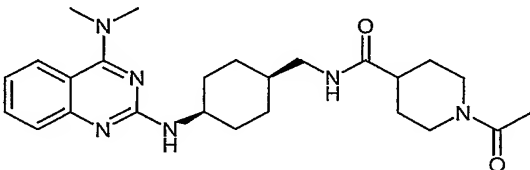
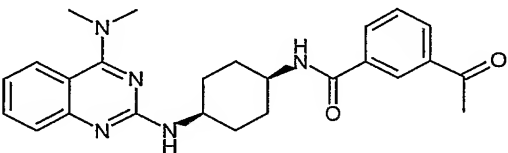
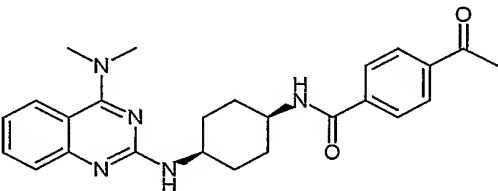
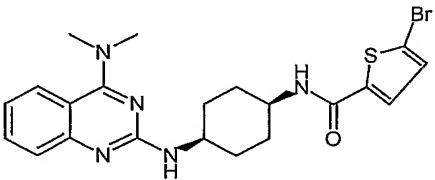
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 562 |  | 490 (M + H) |
| 563 |  | 432 (M + H) |
| 564 |  | 637 (M + H) |
| 565 |  | 632 (M + H) |
| 566 |  | 498 (M + H) |

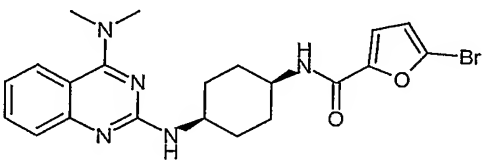
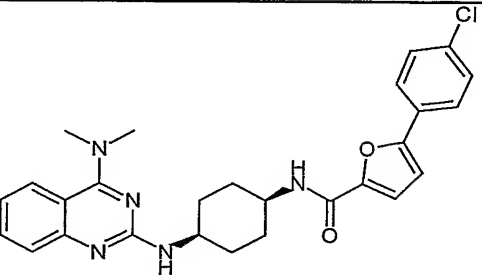
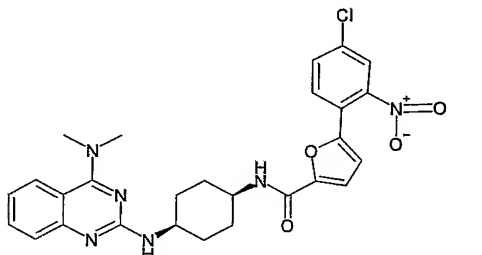
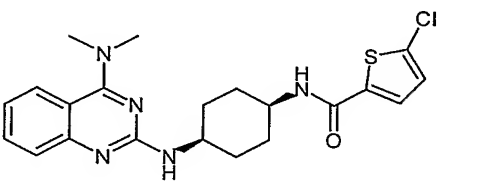
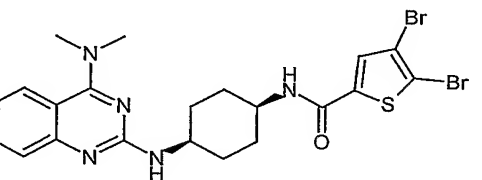
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 567 |  | 475 (M + H) |
| 568 |  | 496 (M + H) |
| 569 |  | 464 (M + H) |
| 570 |  | 468 (M + H) |
| 571 |  | 444 (M + H) |

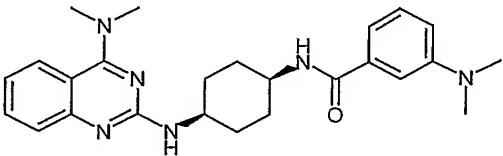
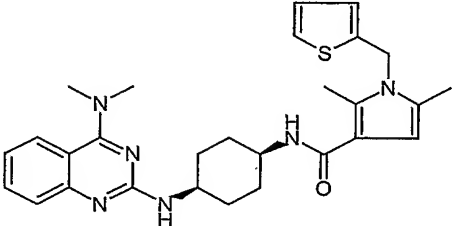
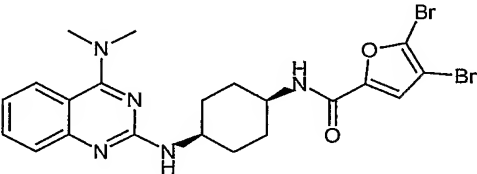
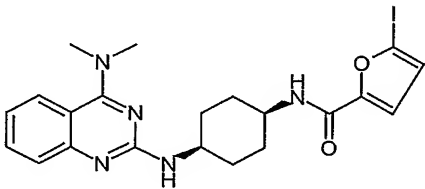
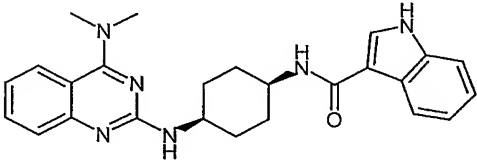
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 572 |  | 496 (M + H) |
| 573 |  | 468 (M + H) |
| 574 |  | 514 (M + H) |
| 575 |  | 492 (M + H) |
| 576 |  | 557 (M + H) |

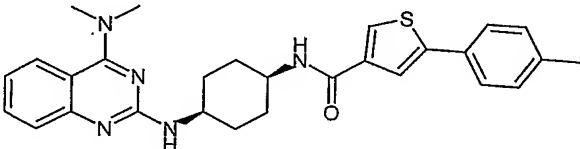
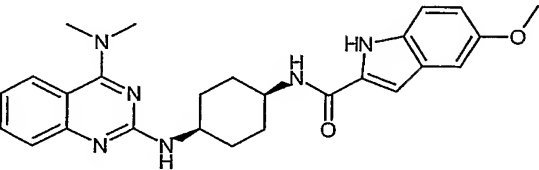
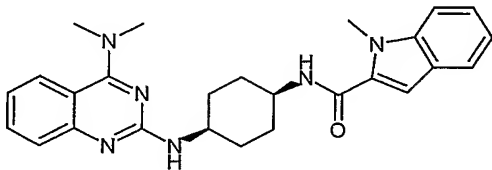
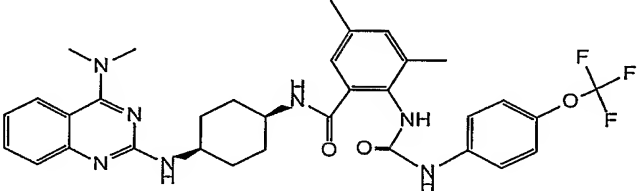
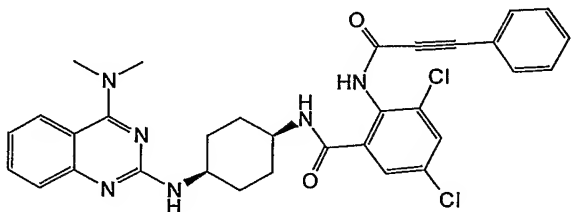
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 577 |  | 516 (M + H) |
| 578 |  | 487 (M + H) |
| 579 |  | 503 (M + H) |
| 580 |  | 342 (M + H) |
| 581 |  | 368 (M + H) |

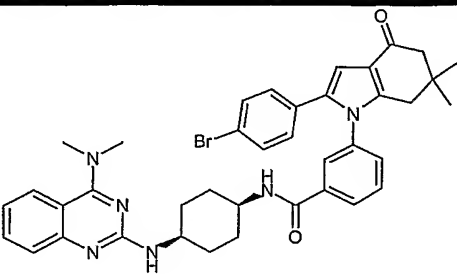
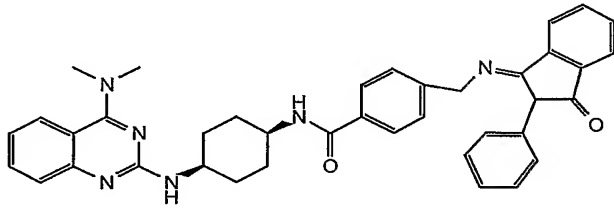
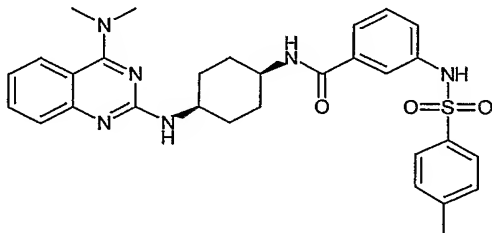
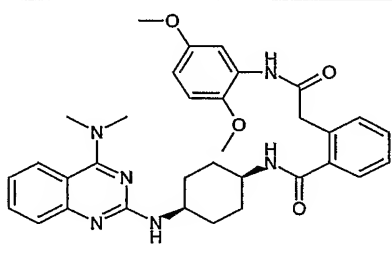
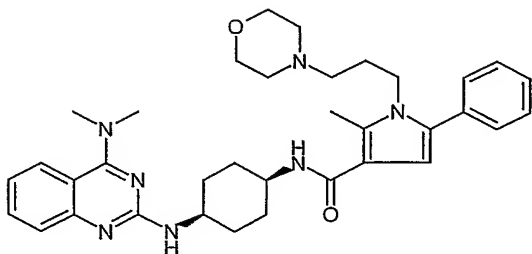
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 582 |  | 410 (M + H) |
| 583 |  | 398 (M + H) |
| 584 |  | 370 (M + H) |
| 585 |  | 413 (M + H) |
| 586 |  | 410 (M + H) |

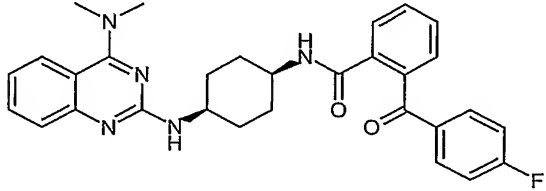
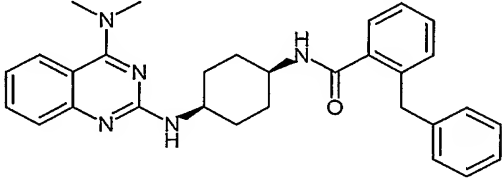
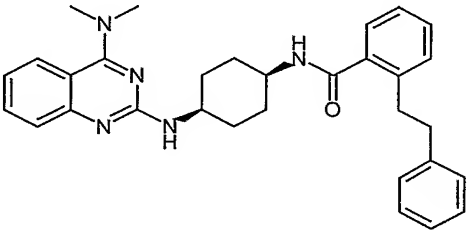
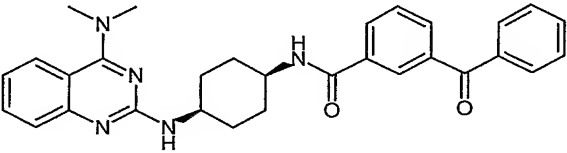
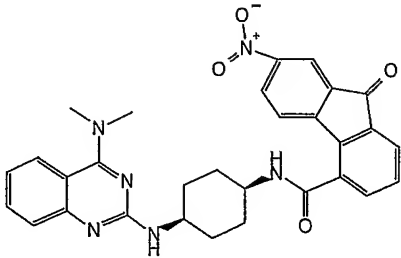
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 587 |  | 398 (M + H) |
| 588 |  | 453 (M + H) |
| 589 |  | 432 (M + H) |
| 590 |  | 432 (M + H) |
| 591 |  | 474 (M + H) |

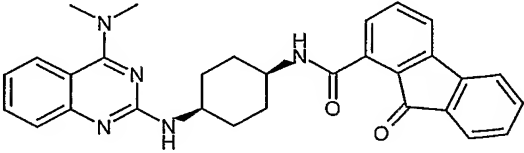
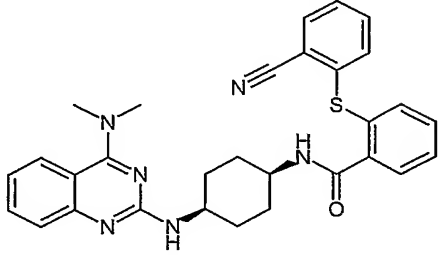
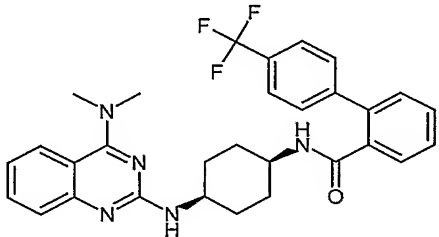
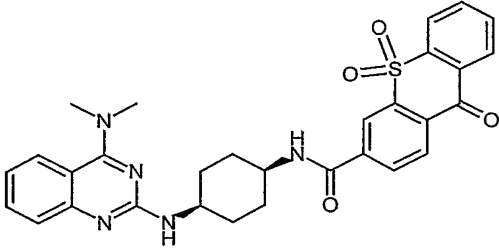
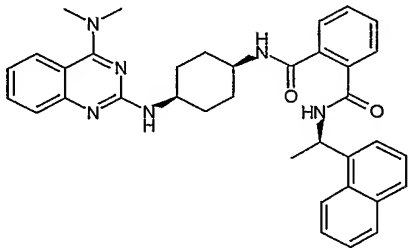
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 592 |  | 458 (M + H) |
| 593 |  | 490 (M + H) |
| 594 |  | 535 (M + H) |
| 595 |  | 430 (M + H) |
| 596 |  | 552 (M + H) |

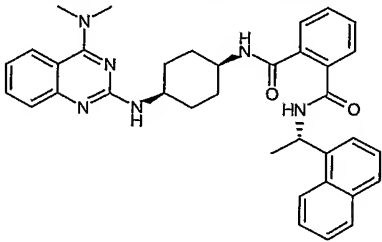
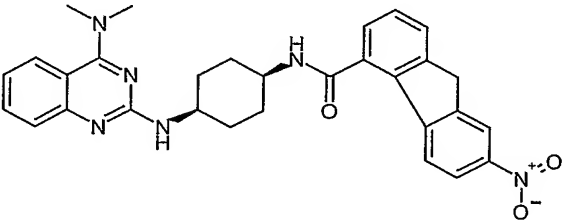
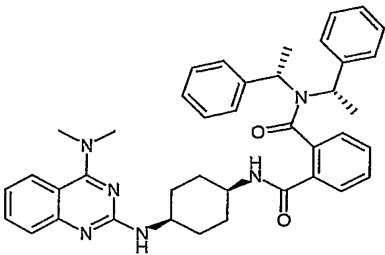
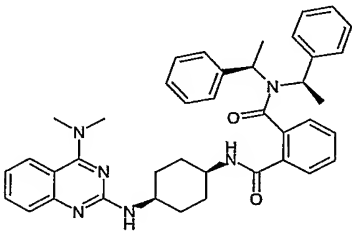
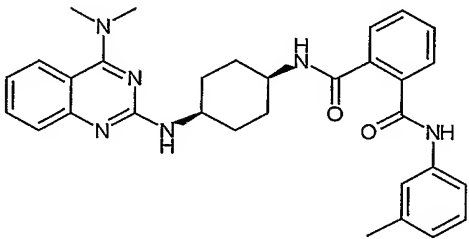
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 597 |  | 433 (M + H) |
| 598 |  | 503 (M + H) |
| 599 |  | 536 (M + H) |
| 600 |  | 506 (M + H) |
| 601 |  | 429 (M + H) |

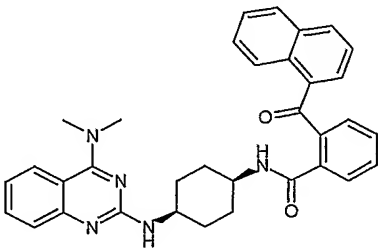
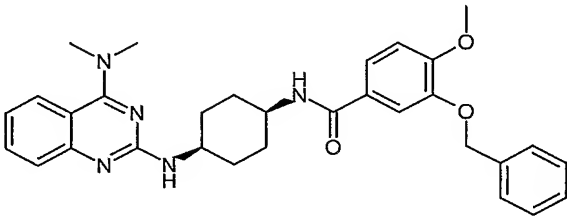
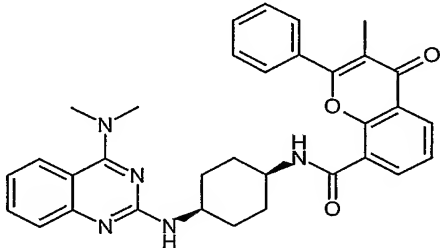
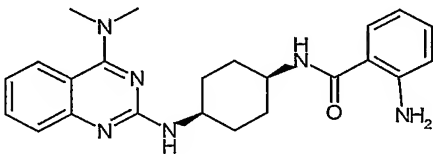
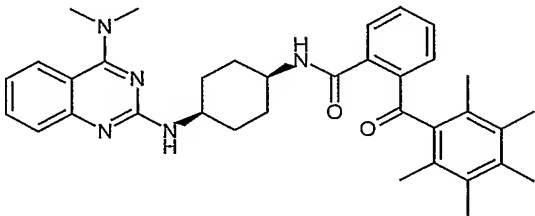
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 602 |  | 486 (M + H) |
| 603 |  | 459 (M + H) |
| 604 |  | 443 (M + H) |
| 605 |  | 636 (M + H) |
| 606 |  | 601 (M + H) |

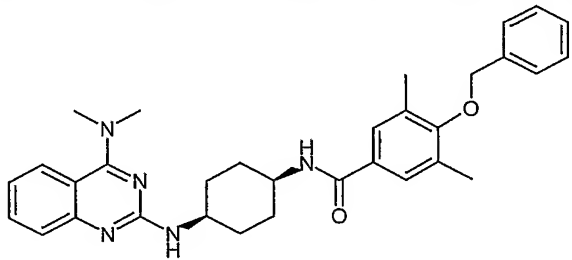
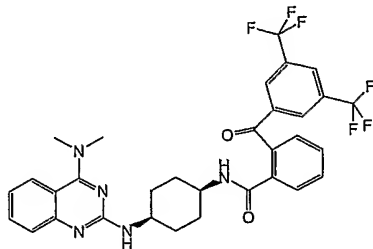
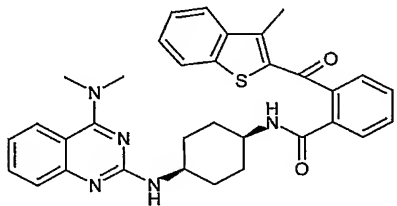
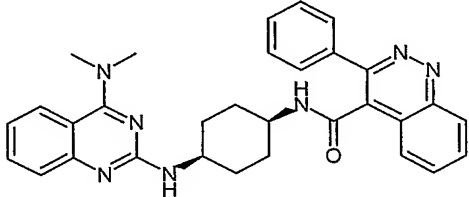
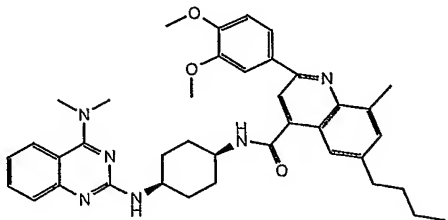
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 607 |  | 705 (M + H) |
| 608 |  | 623 (M + H) |
| 609 |  | 559 (M + H) |
| 610 |  | 583 (M + H) |
| 611 |  | 596 (M + H) |

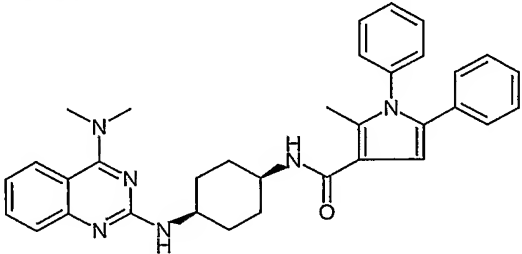
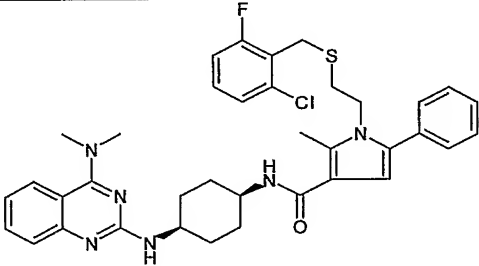
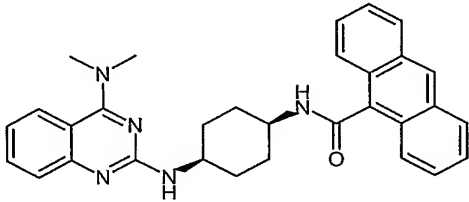
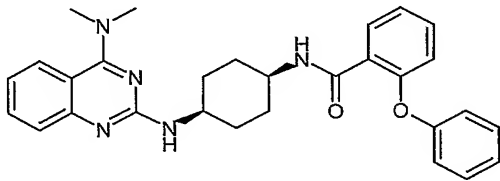
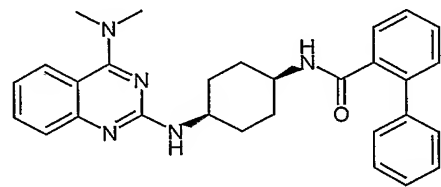
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 612 |  | 512 (M + H) |
| 613 |  | 480 (M + H) |
| 614 |  | 494 (M + H) |
| 615 |  | 494 (M + H) |
| 616 |  | 537 (M + H) |

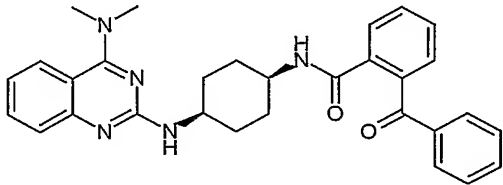
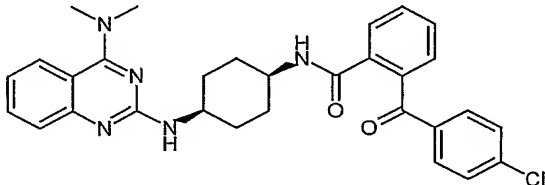
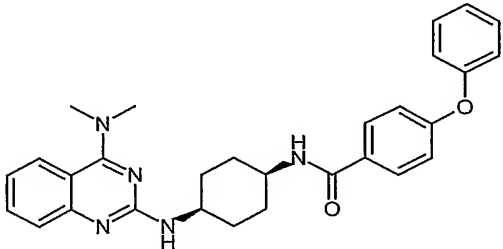
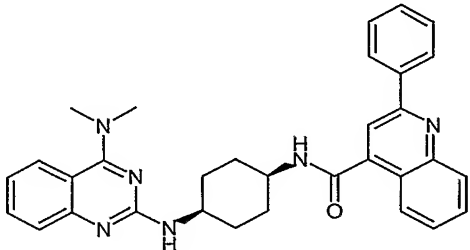
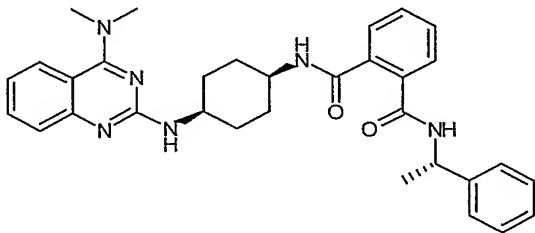
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 617 |  | 492 (M + H) |
| 618 |  | 523 (M + H) |
| 619 |  | 534 (M + H) |
| 620 |  | 556 (M + H) |
| 621 |  | 587 (M + H) |

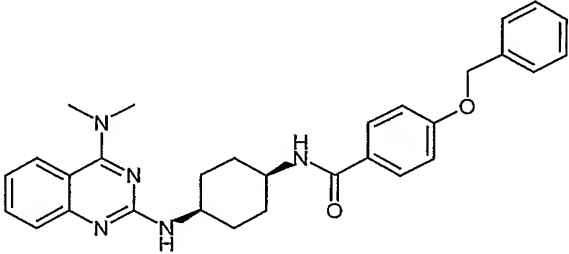
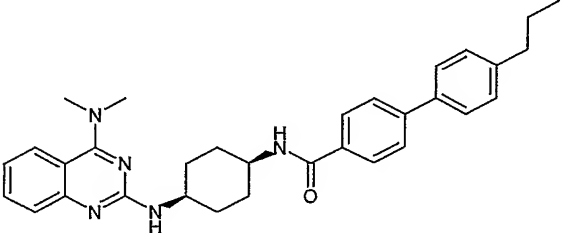
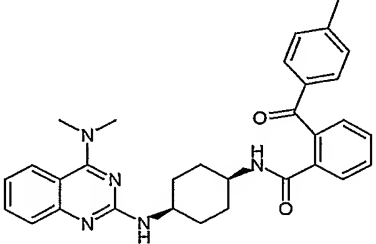
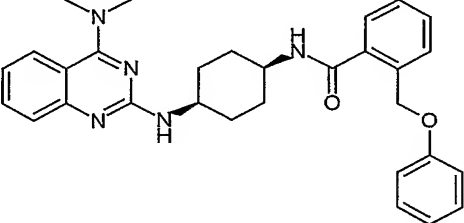
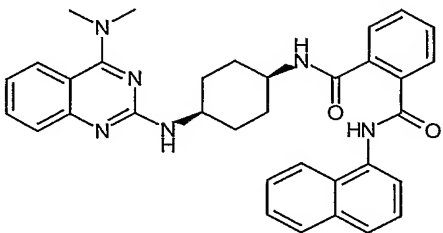
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 622 |  | 587 (M + H) |
| 623 |  | 523 (M + H) |
| 624 |  | 641 (M + H) |
| 625 |  | 641 (M + H) |
| 626 |  | 523 (M + H) |

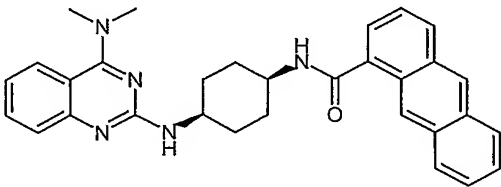
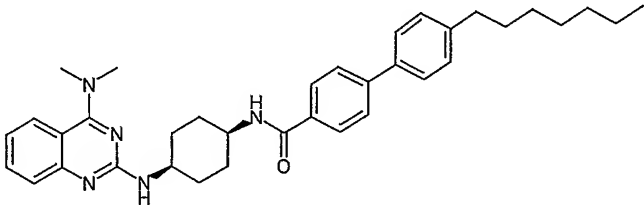
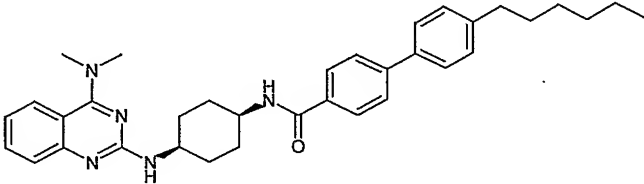
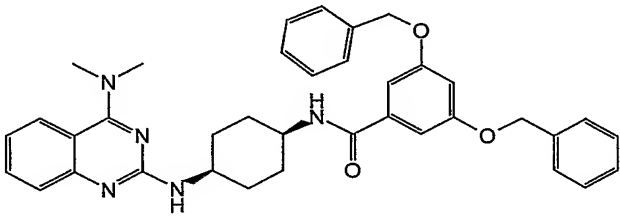
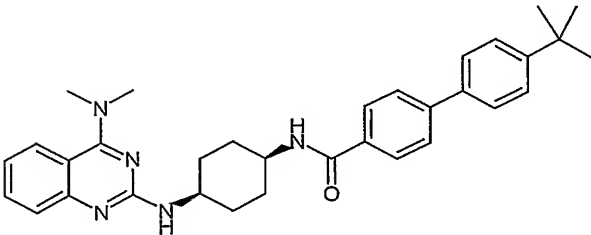
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 627 |  | 544 (M + H) |
| 628 |  | 526 (M + H) |
| 629 |  | 548 (M + H) |
| 630 |  | 405 (M + H) |
| 631 |  | 564 (M + H) |

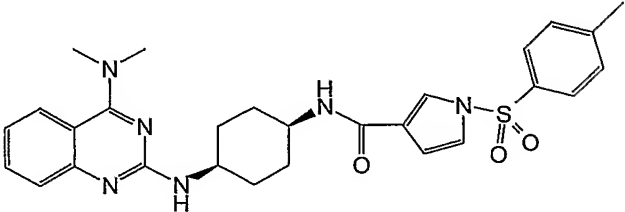
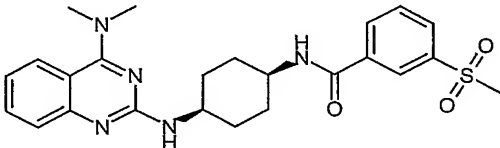
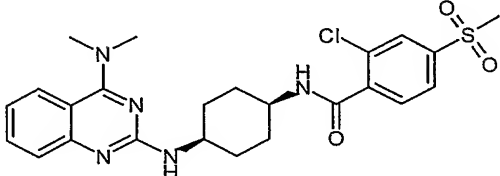
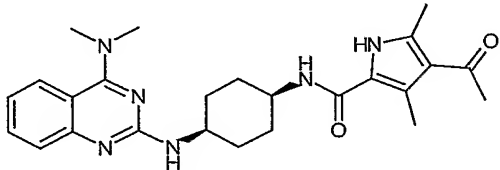
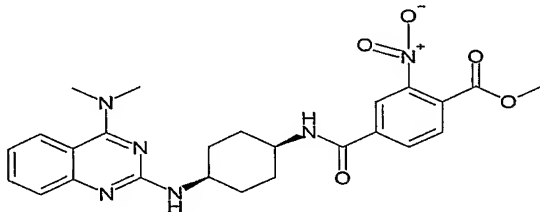
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 632 |  | 524 (M + H) |
| 633 |  | 630 (M + H) |
| 634 |  | 564 (M + H) |
| 635 |  | 518 (M + H) |
| 636 |  | 647 (M + H) |

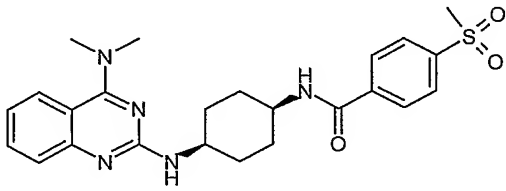
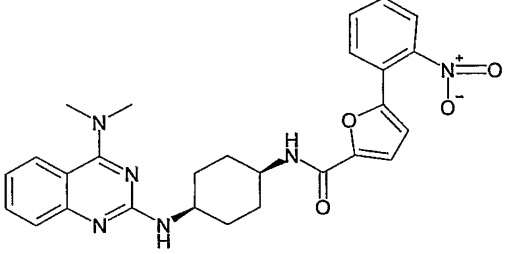
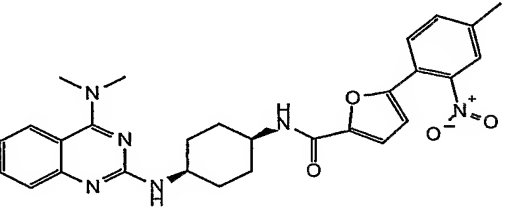
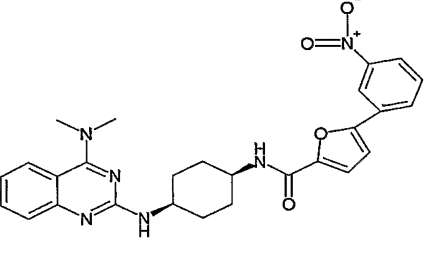
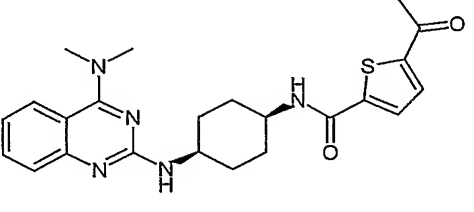
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 637 |  | 545 (M + H) |
| 638 |  | 671 (M + H) |
| 639 |  | 490 (M + H) |
| 640 |  | 482 (M + H) |
| 641 |  | 466 (M + H) |

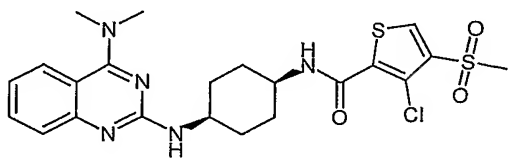
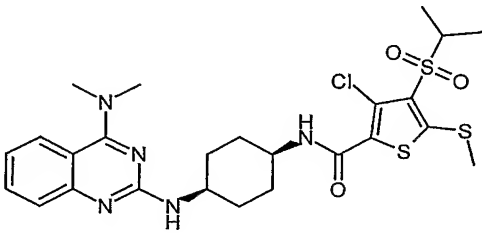
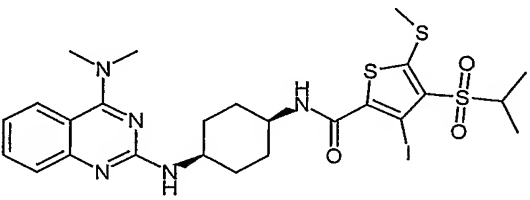
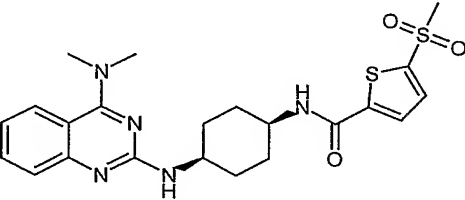
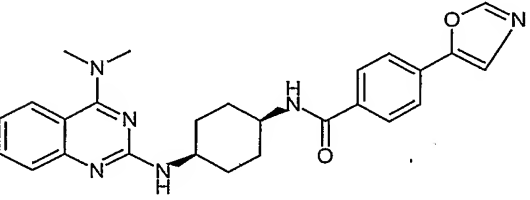
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 642 |  | 494 (M + H) |
| 643 |  | 528 (M + H) |
| 644 |  | 482 (M + H) |
| 645 |  | 517 (M + H) |
| 646 |  | 537 (M + H) |

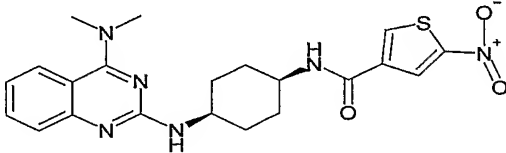
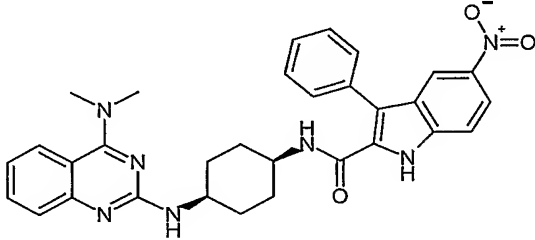
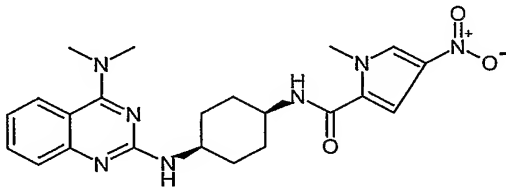
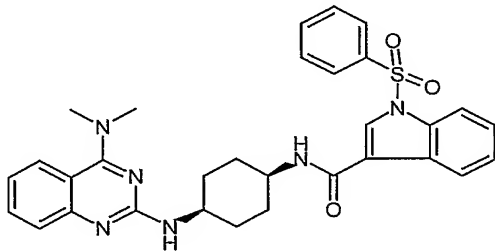
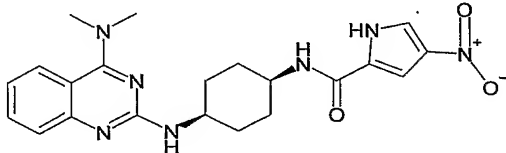
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 647 |  | 496 (M + H) |
| 648 |  | 508 (M + H) |
| 649 |  | 508 (M + H) |
| 650 |  | 496 (M + H) |
| 651 |  | 559 (M + H) |

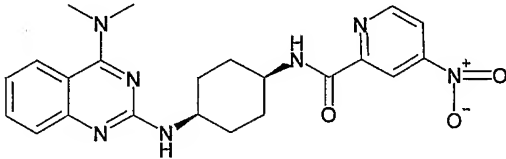
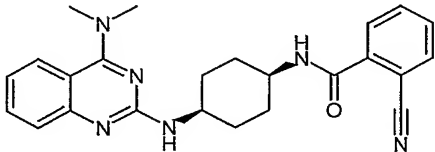
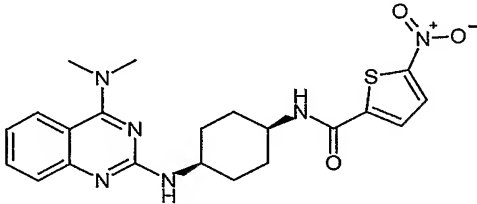
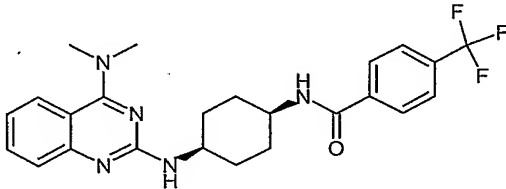
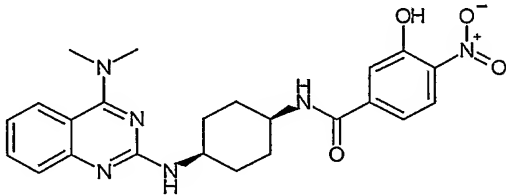
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 652 |  | 490 (M + H) |
| 653 |  | 564 (M + H) |
| 654 |  | 550 (M + H) |
| 655 |  | 602 (M + H) |
| 656 |  | 522 (M + H) |

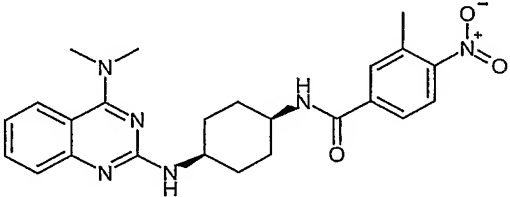
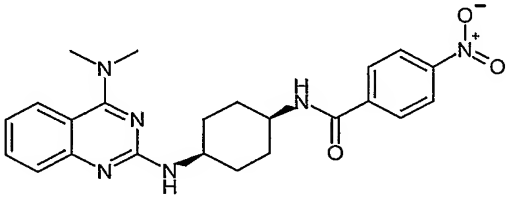
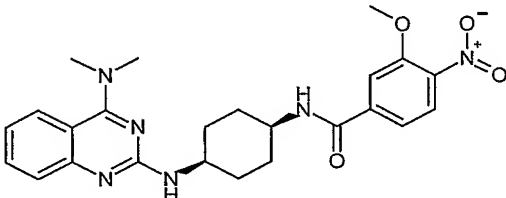
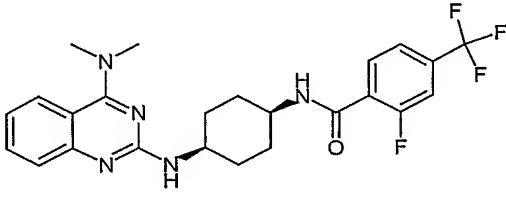
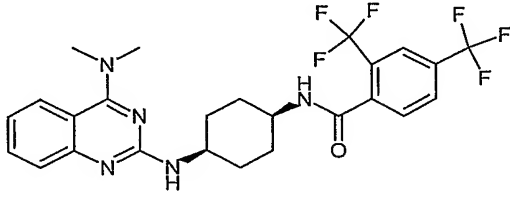
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 657 |  | 533 (M + H) |
| 658 |  | 468 (M + H) |
| 659 |  | 502 (M + H) |
| 660 |  | 449 (M + H) |
| 661 |  | 493 (M + H) |

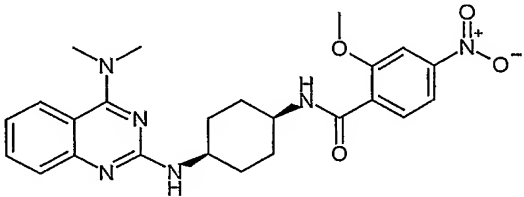
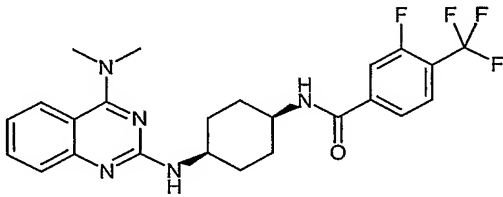
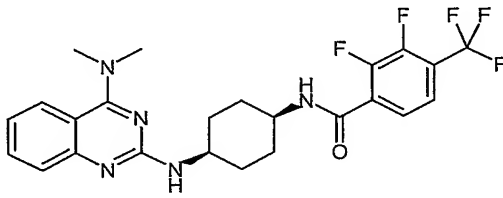
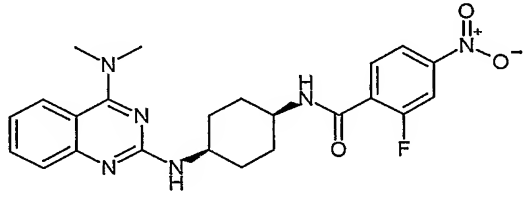
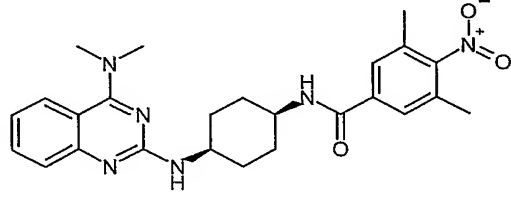
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 662 |  | 468 (M + H) |
| 663 |  | 501 (M + H) |
| 664 |  | 515 (M + H) |
| 665 |  | 501 (M + H) |
| 666 |  | 438 (M + H) |

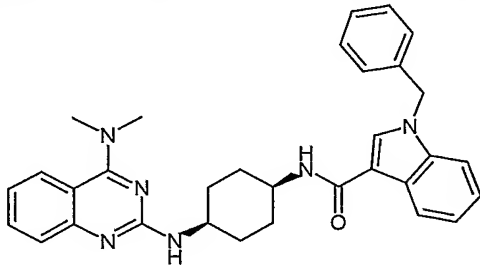
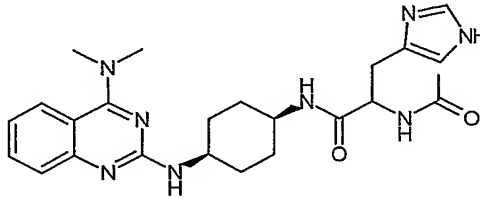
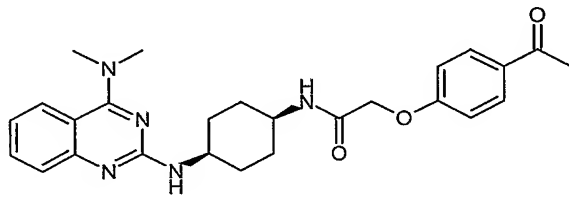
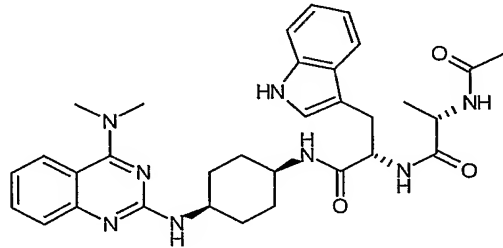
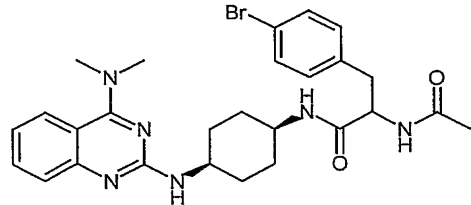
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 667 |  | 508 (M + H) |
| 668 |  | 582 (M + H) |
| 669 |  | 674 (M + H) |
| 670 |  | 474 (M + H) |
| 671 |  | 457 (M + H) |

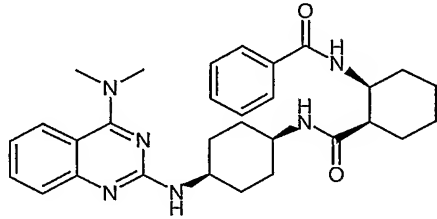
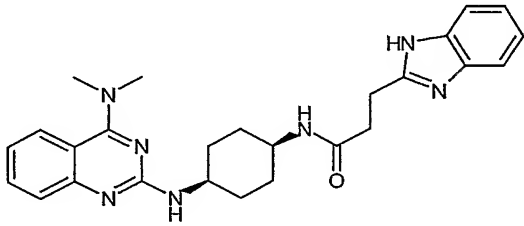
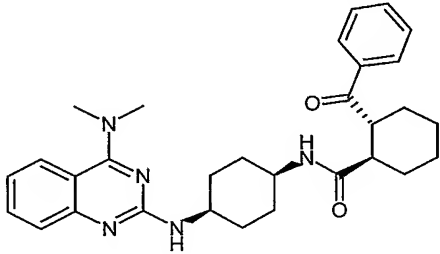
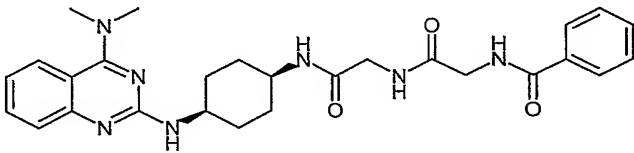
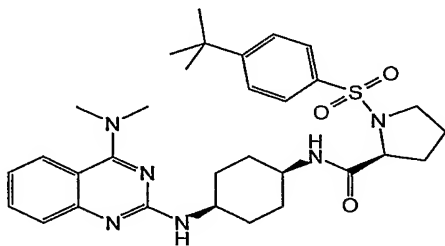
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 672 |  | 441 (M + H) |
| 673 |  | 550 (M + H) |
| 674 |  | 438 (M + H) |
| 675 |  | 569 (M + H) |
| 676 |  | 424 (M + H) |

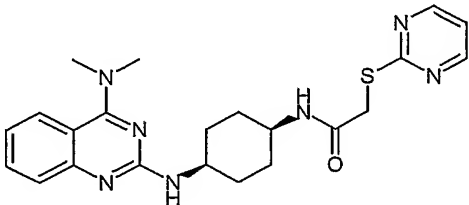
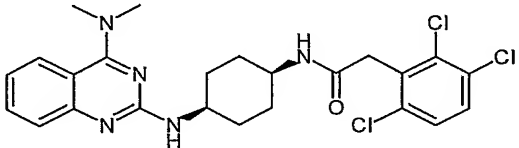
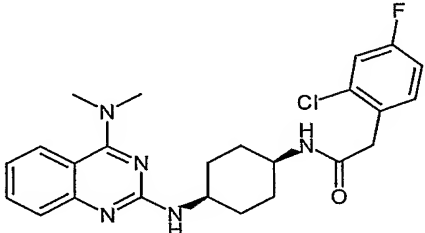
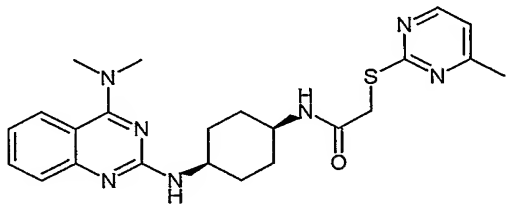
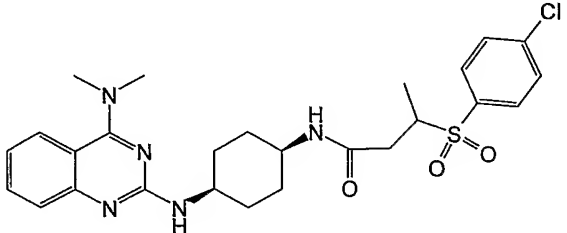
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 677 |  | 436 (M + H) |
| 678 |  | 415 (M + H) |
| 679 |  | 441 (M + H) |
| 680 |  | 458 (M + H) |
| 681 |  | 451 (M + H) |

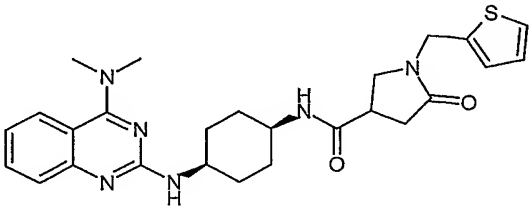
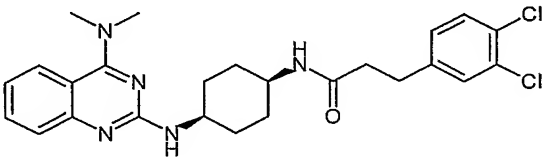
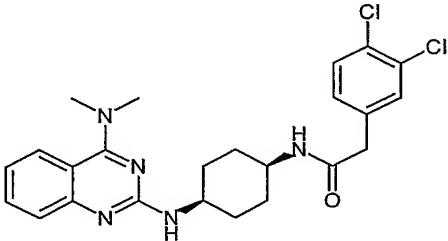
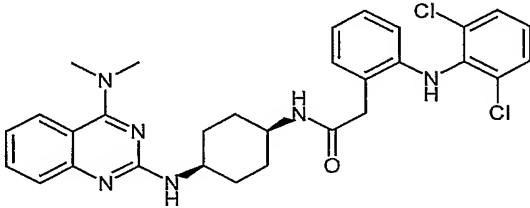
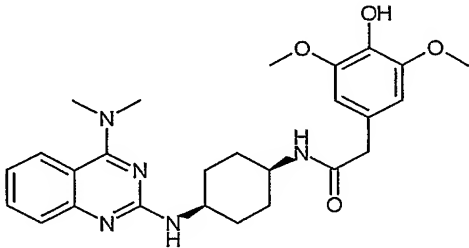
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 682 |  | 449 (M + H) |
| 683 |  | 435 (M + H) |
| 684 |  | 465 (M + H) |
| 685 |  | 476 (M + H) |
| 686 |  | 526 (M + H) |

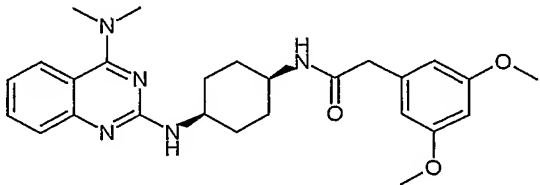
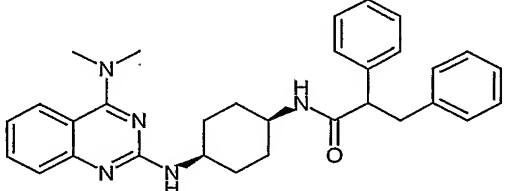
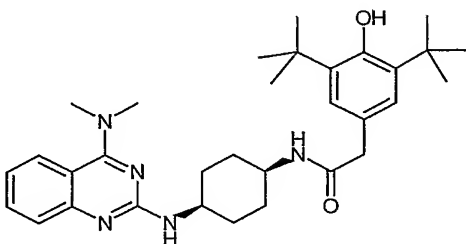
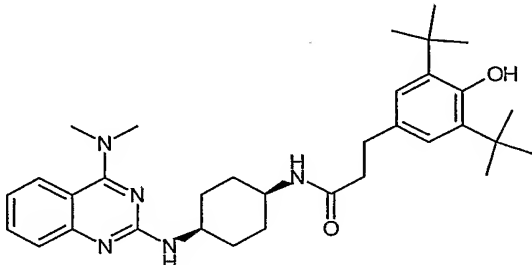
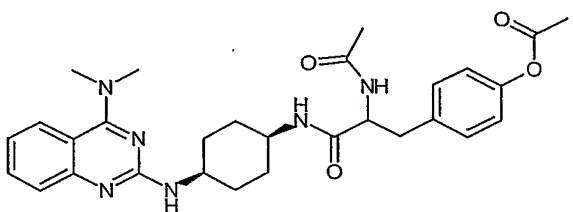
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 687 |  | 465 (M + H) |
| 688 |  | 476 (M + H) |
| 689 |  | 494 (M + H) |
| 690 |  | 453 (M + H) |
| 691 |  | 463 (M + H) |

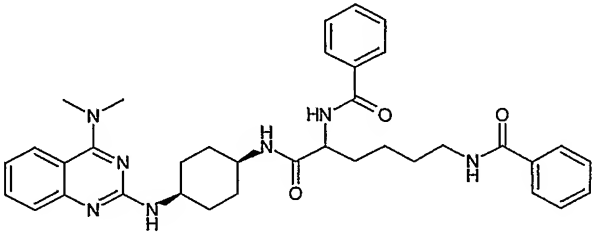
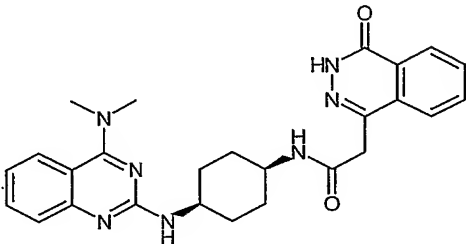
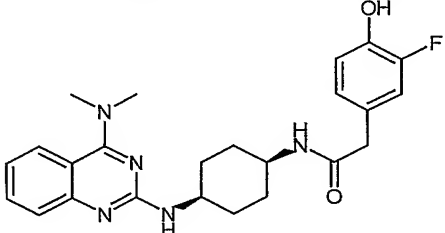
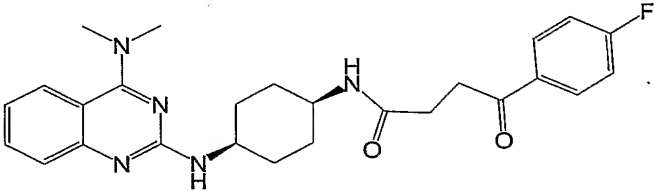
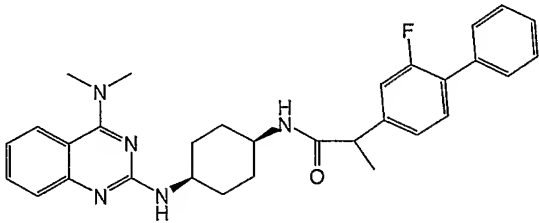
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 692 |  | 519 (M + H) |
| 693 |  | 465 (M + H) |
| 694 |  | 462 (M + H) |
| 695 |  | 585 (M + H) |
| 696 |  | 553 (M + H) |

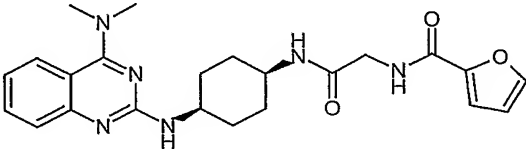
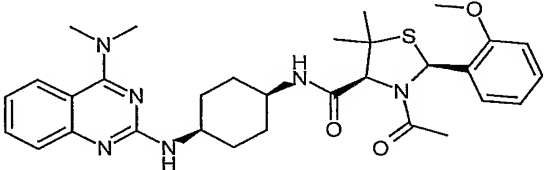
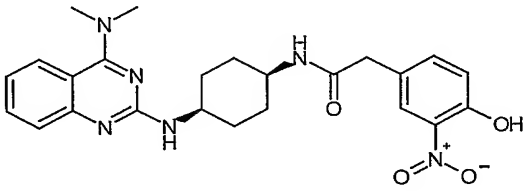
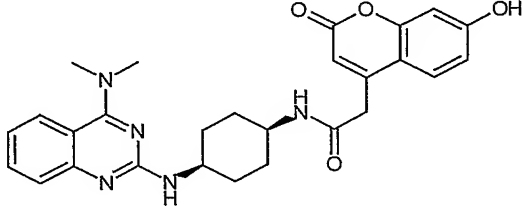
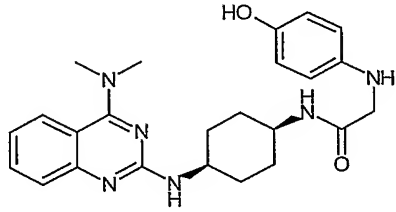
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 697 |  | 515 (M + H) |
| 698 |  | 458 (M + H) |
| 699 |  | 500 (M + H) |
| 700 |  | 504 (M + H) |
| 701 |  | 579 (M + H) |

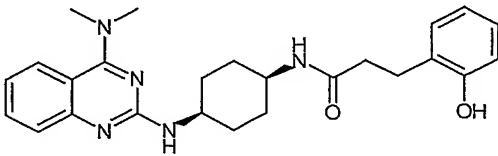
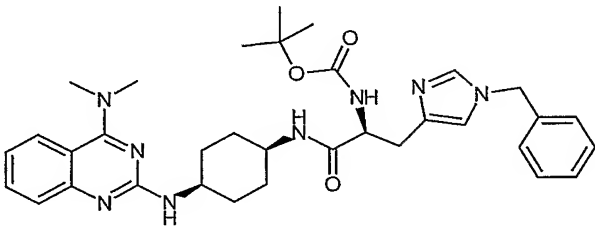
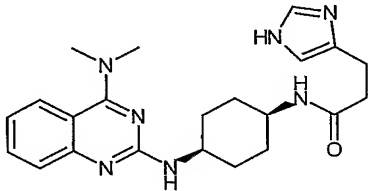
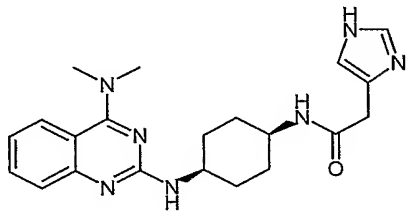
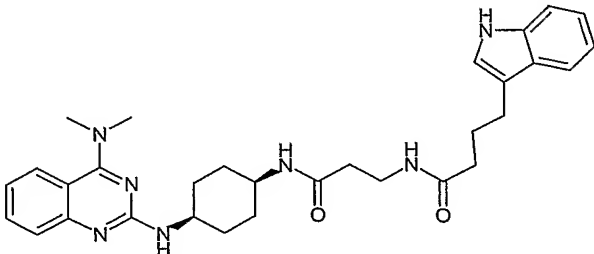
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 702 |  | 438 (M + H) |
| 703 |  | 506 (M + H) |
| 704 |  | 456 (M + H) |
| 705 |  | 452 (M + H) |
| 706 |  | 530 (M + H) |

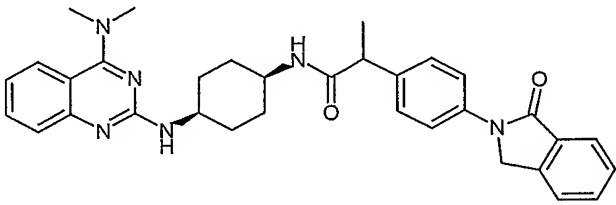
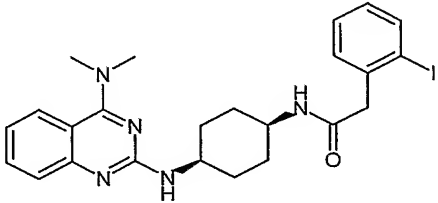
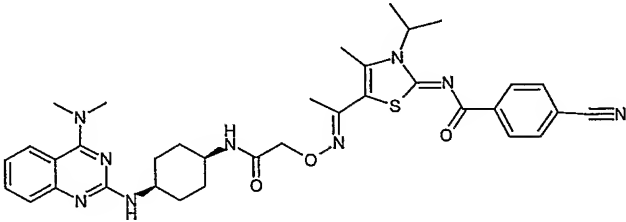
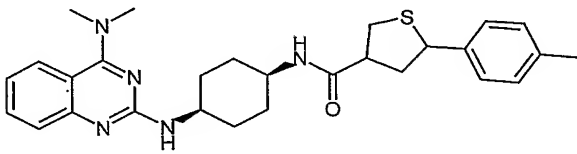
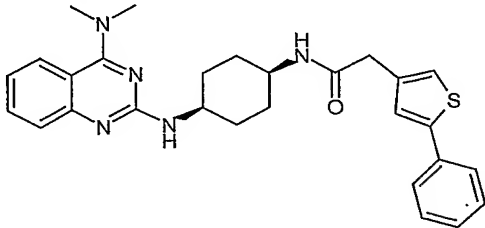
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 707 |  | 493 (M + H) |
| 708 |  | 486 (M + H) |
| 709 |  | 472 (M + H) |
| 710 |  | 563 (M + H) |
| 711 |  | 480 (M + H) |

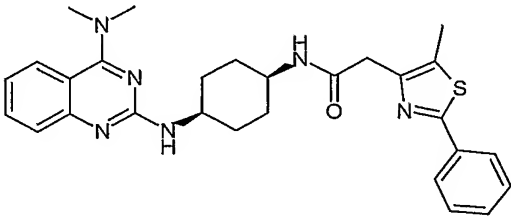
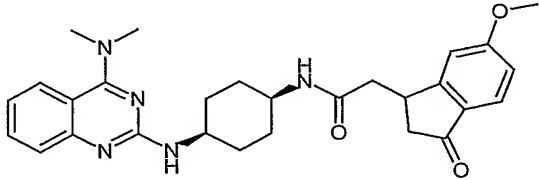
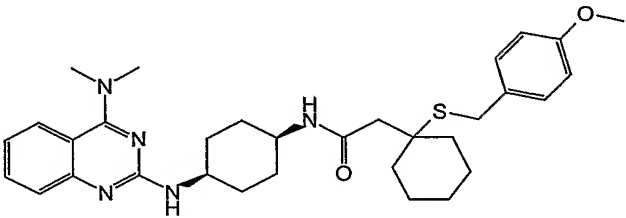
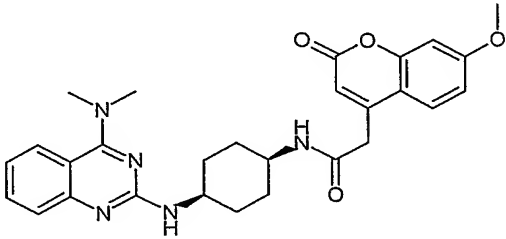
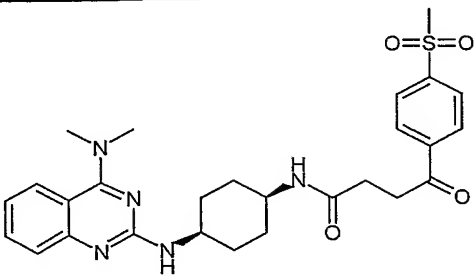
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 712 |  | 464 (M + H) |
| 713 |  | 494 (M + H) |
| 714 |  | 532 (M + H) |
| 715 |  | 546 (M + H) |
| 716 |  | 533 (M + H) |

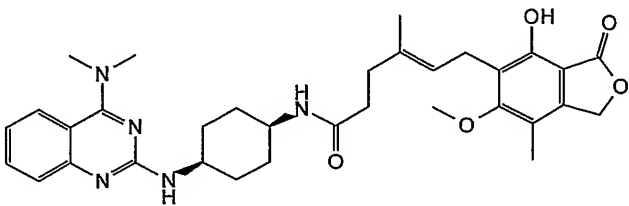
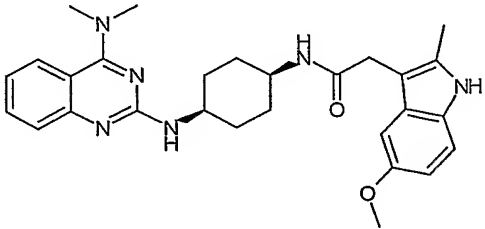
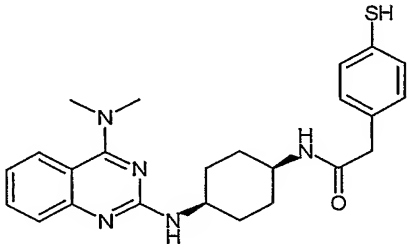
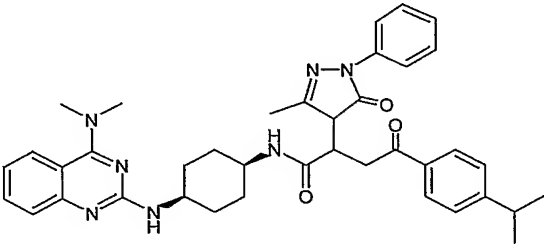
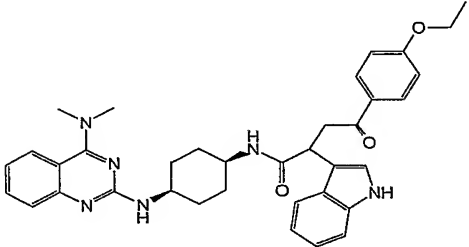
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 717 |  | 622 (M + H) |
| 718 |  | 472 (M + H) |
| 719 |  | 438 (M + H) |
| 720 |  | 464 (M + H) |
| 721 |  | 512 (M + H) |

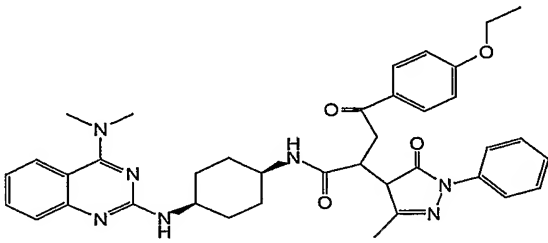
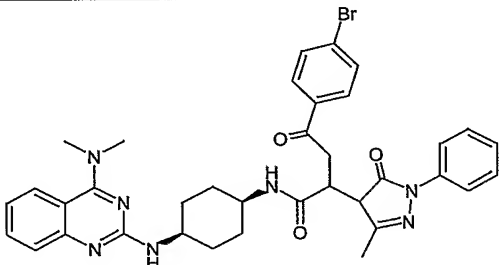
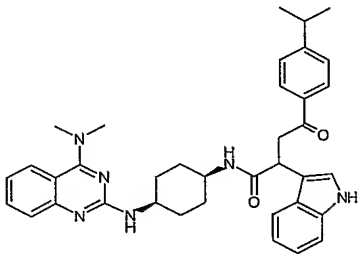
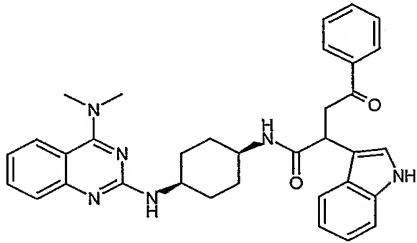
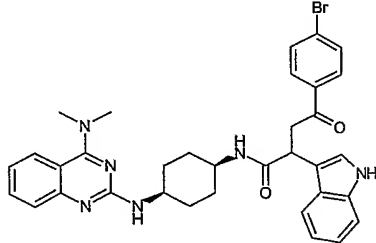
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 722 |  | 437 (M + H) |
| 723 |  | 577 (M + H) |
| 724 |  | 465 (M + H) |
| 725 |  | 488 (M + H) |
| 726 |  | 435 (M + H) |

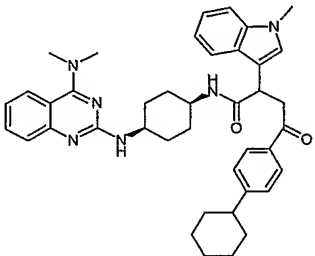
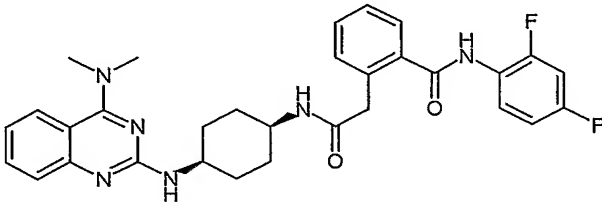
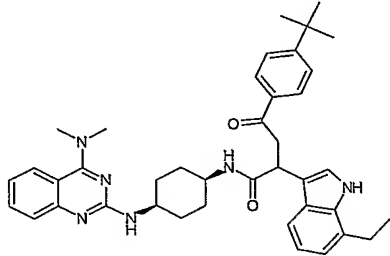
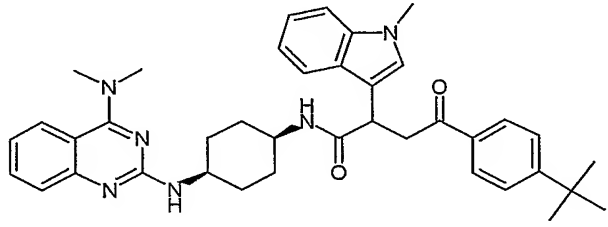
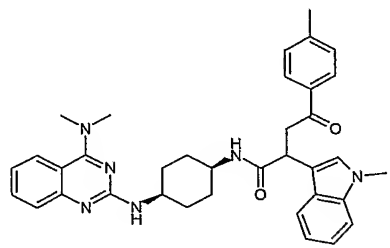
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 727 |  | 434 (M + H) |
| 728 |  | 613 (M + H) |
| 729 |  | 408 (M + H) |
| 730 |  | 394 (M + H) |
| 731 |  | 542 (M + H) |

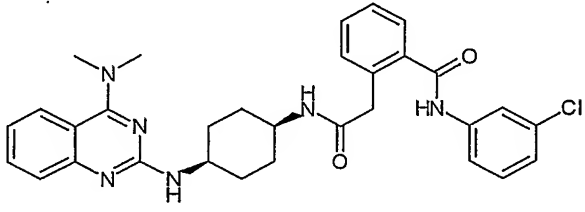
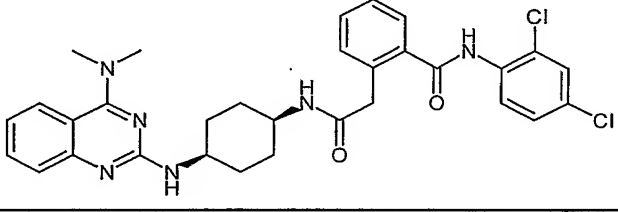
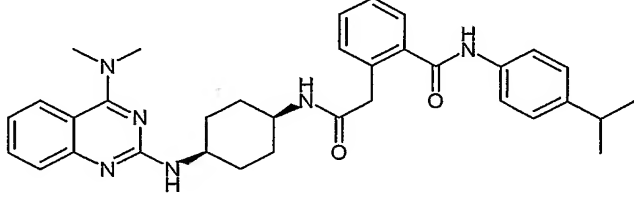
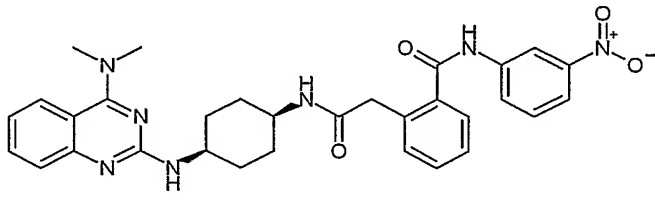
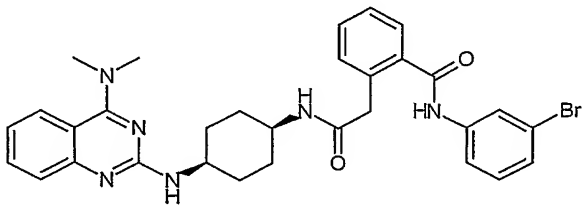
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 732 |  | 549 (M + H) |
| 733 |  | 530 (M + H) |
| 734 |  | 668 (M + H) |
| 735 |  | 490 (M + H) |
| 736 |  | 486 (M + H) |

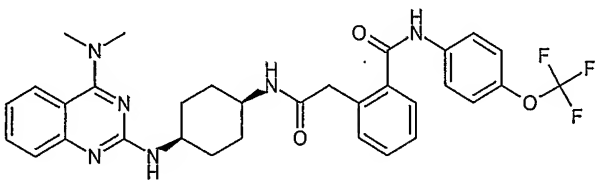
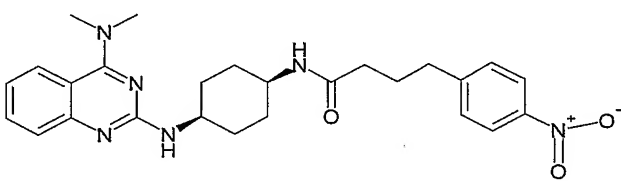
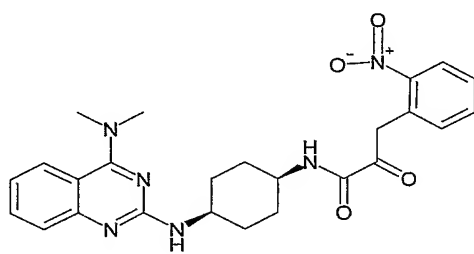
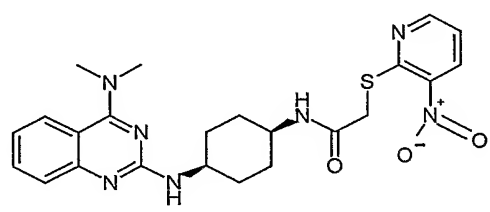
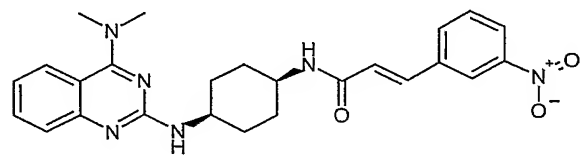
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 737 |  | 501 (M + H) |
| 738 |  | 488 (M + H) |
| 739 |  | 562 (M + H) |
| 740 |  | 502 (M + H) |
| 741 |  | 524 (M + H) |

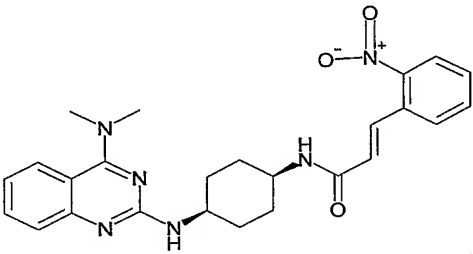
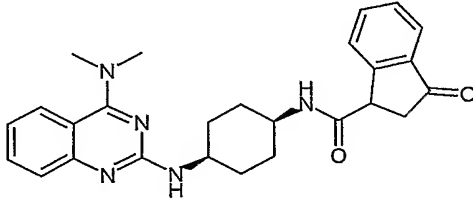
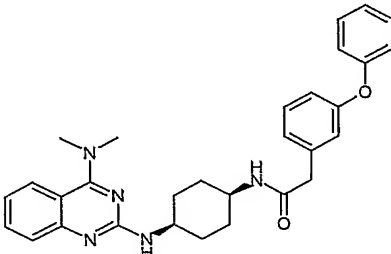
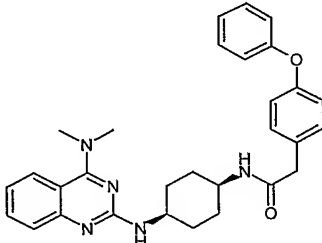
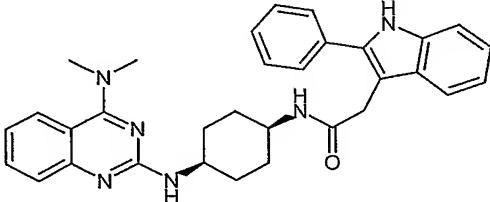
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 742 |  | 588 (M + H) |
| 743 |  | 487 (M + H) |
| 744 |  | 436 (M + H) |
| 745 |  | 660 (M + H) |
| 746 |  | 605 (M + H) |

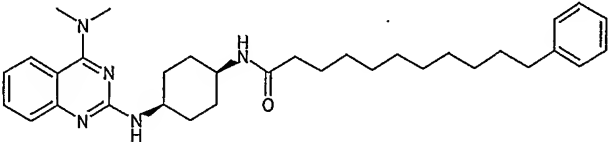
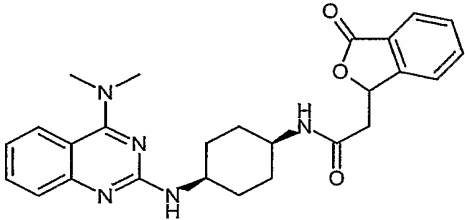
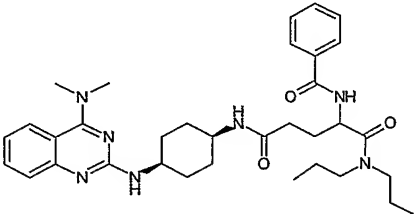
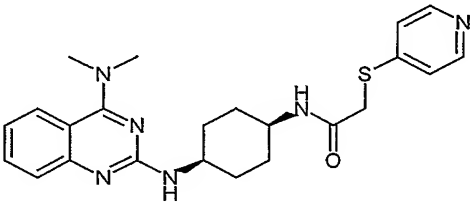
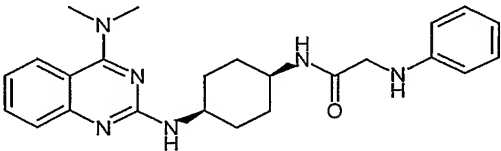
| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 747 |  | 662 (M + H) |
| 748 |  | 696 (M + H) |
| 749 |  | 603 (M + H) |
| 750 |  | 561 (M + H) |
| 751 |  | 639 (M + H) |

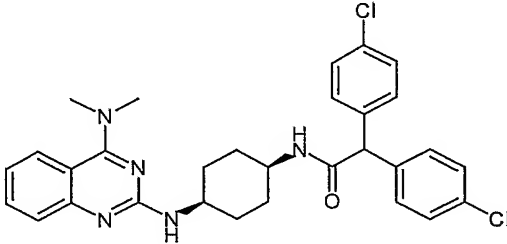
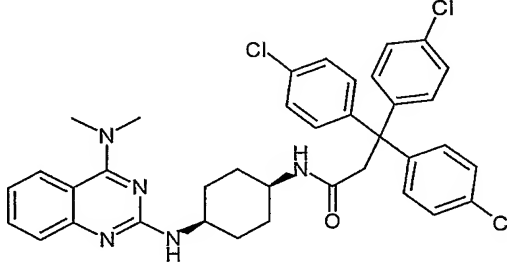
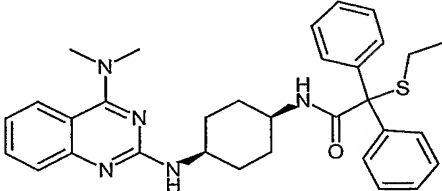
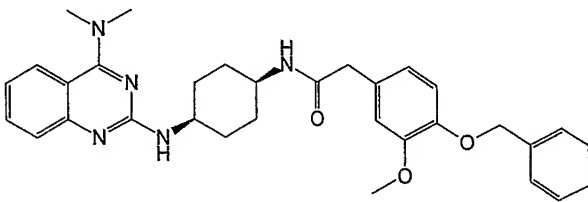
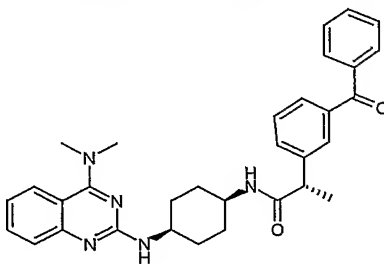
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 752 |  | 657 (M + H) |
| 753 |  | 559 (M + H) |
| 754 |  | 645 (M + H) |
| 755 |  | 631 (M + H) |
| 756 |  | 589 (M + H) |

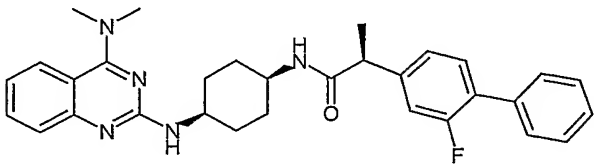
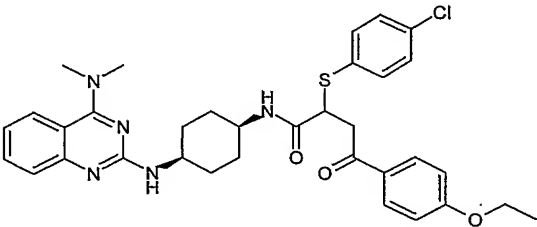
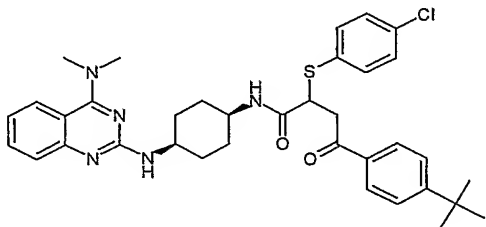
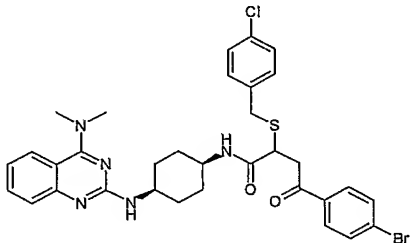
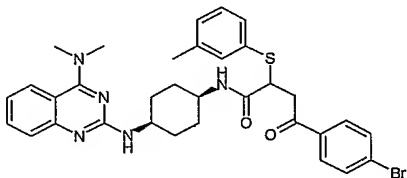
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 757 |  | 557 (M + H) |
| 758 |  | 591 (M + H) |
| 759 |  | 565 (M + H) |
| 760 |  | 568 (M + H) |
| 761 |  | 601 (M + H) |

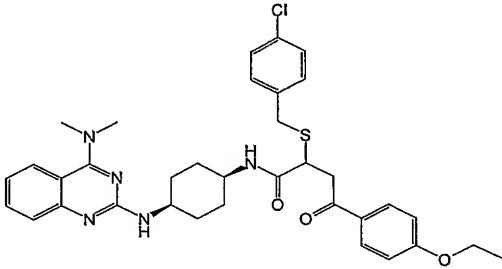
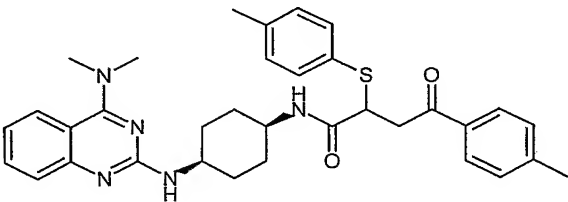
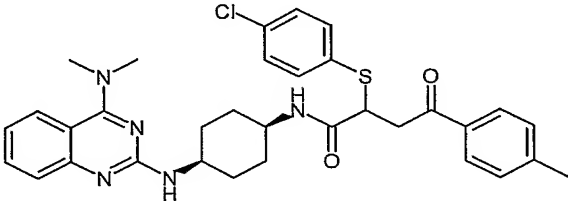
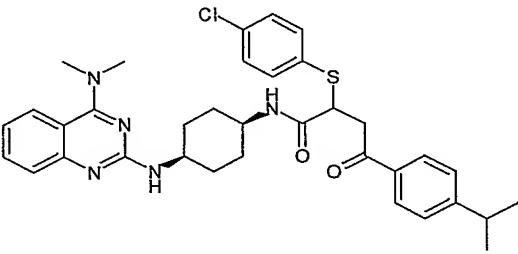
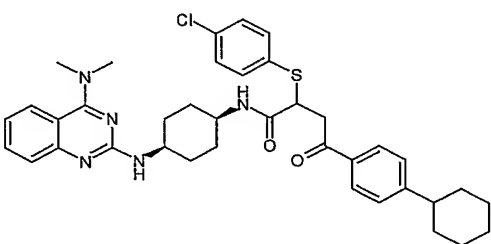
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 762 |  | 607 (M + H) |
| 763 |  | 477 (M + H) |
| 764 |  | 477 (M + H) |
| 765 |  | 482 (M + H) |
| 766 |  | 461 (M + H) |

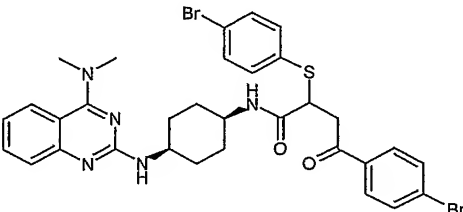
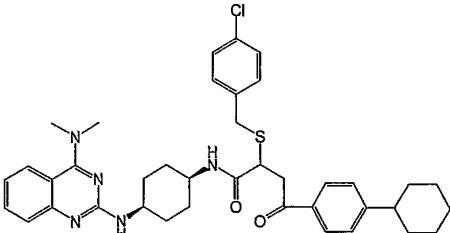
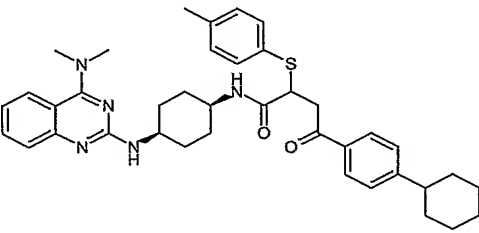
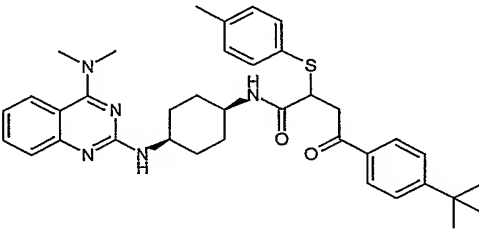
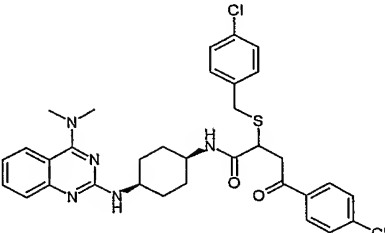
| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 767 |  | 461 (M + H) |
| 768 |  | 444 (M + H) |
| 769 |  | 496 (M + H) |
| 770 |  | 496 (M + H) |
| 771 |  | 519 (M + H) |

| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 772 |  | 530 (M + H) |
| 773 |  | 460 (M + H) |
| 774 |  | 602 (M + H) |
| 775 |  | 437 (M + H) |
| 776 |  | 419 (M + H) |

| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 777 |  | 548 (M + H) |
| 778 |  | 672 (M + H) |
| 779 |  | 540 (M + H) |
| 780 |  | 540 (M + H) |
| 781 |  | 522 (M + H) |

| Example No. | Structure | APCI-MS |
|-------------|---|-------------|
| 782 |  | 512 (M + H) |
| 783 |  | 632 (M + H) |
| 784 |  | 644 (M + H) |
| 785 |  | 680 (M + H) |
| 786 |  | 646 (M + H) |

| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 787 |  | 646 (M + H) |
| 788 |  | 582 (M + H) |
| 789 |  | 602 (M + H) |
| 790 |  | 630 (M + H) |
| 791 |  | 670 (M + H) |

| Example No. | Structure | APCI-MS |
|-------------|--|-------------|
| 792 |  | 710 (M + H) |
| 793 |  | 684 (M + H) |
| 794 |  | 650 (M + H) |
| 795 |  | 624 (M + H) |
| 796 |  | 636 (M + H) |